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THE JOURNAL OF CLINICAL ENDOCRINOLOGY

VOLUME 8 NUMBER 5

Next Annual Meeting, Palmer House, Chicago, June 18-19, 1948

MAY 1948

CLASSIFICATION OF MALE HYPOGONADISM AND A DISCUSSION OF THE PATHOLOGIC PHYSIOLOGY, DIAGNOSIS AND TREATMENT . . . 345
Carl G. Heller and Warren O. Nelson

MALE PSEUDOHERMAPHRODITISM PROVED BY SURGICAL EXPLORATION AND MICROSCOPIC EXAMINATION. A CASE REPORT WITH SPECULATIONS CONCERNING PATHOGENESIS 367
Minnie B. Goldberg and Alice F. Maxwell

THE RELATION BETWEEN INFANT BIRTHWEIGHT AND SUBSEQUENT DEVELOPMENT OF MATERNAL DIABETES MELLITUS 380
Joseph P. Kriss and Palmer H. Futcher

EXTREME LEYDIG CELL HYPERPLASIA ASSOCIATED WITH TWO OTHER ENDOCRINE CHANGES. A CASE REPORT 390
E. Lloyd Wilbur and Robert A. Burger

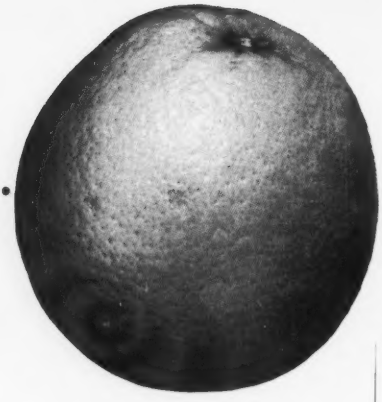
NECROPSY STUDY OF A CASE OF TURNER'S SYNDROME. A CASE REPORT 397
A. Atria, R. Sanz and S. Donoso

INDUCTION OF UTERINE BLEEDING IN AMENORRHEA WITH A SINGLE INJECTION OF PRECIPITATES OF ESTRONE AND PROGESTERONE 406
Bernhard Zondek and Samuel Rozin

THE THIRTIETH ANNUAL MEETING OF THE ASSOCIATION 413

PROGRAM OF THE 1948 LAURENTIAN HORMONE CONFERENCE 421

Issued monthly for The Association for the Study of Internal Secretions by Charles C Thomas, Publisher. Annual subscription, $6.50; single copies, $1.00



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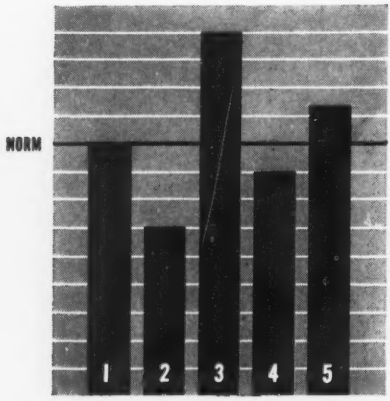

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CLASSIFICATION OF MALE HYPOGONADISM AND A DISCUSSION OF THE PATHOLOGIC PHYSIOLOGY, DIAGNOSIS AND TREATMENT*

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INTRODUCTION

CLASSIFICATION, diagnosis and treatment of testicular failure have been radically altered and at the same time have been placed on a rational basis by the introduction of two important technics: 1) determining the alterations in microscopic anatomy of the testis from a study of biopsy specimens, and 2) determining the urinary excretion of pituitary gonadotropic hormones. The biopsy studies reveal whether the testicular

Received for publication October 30, 1947.

* Read in part before the annual meeting of the Central Society for Clinical Research, Chicago, Illinois, November, 1942 (Abst. *J.A.M.A.* 121: 1176, 1943) and in part before a meeting of the North Pacific Society of Internal Medicine, Portland, Oregon, October 27, 1945.

The patients comprising the basis of this dissertation were studied at Wayne University College of Medicine and the City of Detroit Receiving Hospital, Detroit, and the Multnomah County Hospital and the University of Oregon Medical School, Portland.

The study was supported in part by a grant from the American College of Physicians, and in part by a grant from the Schering Corporation, Bloomfield, New Jersey, through the courtesy of Dr. Edward Henderson.

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‡ Professor of Anatomy.

lesion involves primarily the seminiferous tubules or the interstitial cells of Leydig. Biopsy studies also indicate the prognosis and treatment insofar as they reveal whether the testicular tissue is irreparably damaged or is potentially capable of being stimulated. The urinary gonadotropins reveal whether the testicular failure is secondary to pituitary failure or whether it is primary. Thus instances of gonadal failure may be divided into two distinct groups: 1) those having distinctly higher than normal titers of gonadotropins—the *hypergonadotropic syndromes*, and 2) those having distinctly subnormal titers of gonadotropins—the *hypogonadotropic syndromes*.

In classifying the true hypogonadal states it is necessary to know whether the deficiency developed after maturity was reached or whether it was present early enough in life to prevent the patient from undergoing puberty. This knowledge permits the separation of cases into two large groups, each of which can be identically subdivided into four physiologic categories, dependent upon the primary site of failure. Thus in each group the hypogonadism may be due to 1) failure of all the functions of the anterior pituitary, 2) failure of the pituitary to elaborate gonadotropic hormone, 3) failure of the interstitial cells of Leydig of the testis, and 4) failure of the seminiferous tubules of the testis.

Failure at each of the four sites will lead to failure of spermatogenesis.

1) When the entire pituitary gland is affected—for example, by atrophy—neither the gonadotropic complex nor the other tropic hormones will be elaborated and consequently the Leydig cells and seminiferous tubules will fail to function. This can be readily understood by referring to the diagram of the physiologic control of the testis (Fig. 1).

2) If only the gonadotropic hormones fail to be secreted by the pituitary, this too will lead to Leydig cell and seminiferous tubule failure.

3) Primary failure of the interstitial cells of Leydig, which normally elaborate androgens, may result in abeyance of spermatogenesis since androgens maintain the seminiferous tubules as well as the rest of the genital tract in a functional state (1).

4) Failure on the part of the seminiferous tubules alone leads to failure of spermatogenesis without signs of hormonal deficiency.

Patients with any of the first three types of hormonal failure will have the usual clinical manifestations of androgen deficiency. If the onset of such failure antedates puberty, the condition will be characterized by changes in the bony skeleton; namely, dwarfism in the case of panhypopituitarism, and eunuchoidism in the other two instances. If the failure occurs after the individual has matured, no skeletal changes and often very little change in secondary sex characteristics will be noted. On clinical grounds alone it is often impossible to determine whether the hypogonadism is the result of primary testicular failure or of primary pituitary fail-

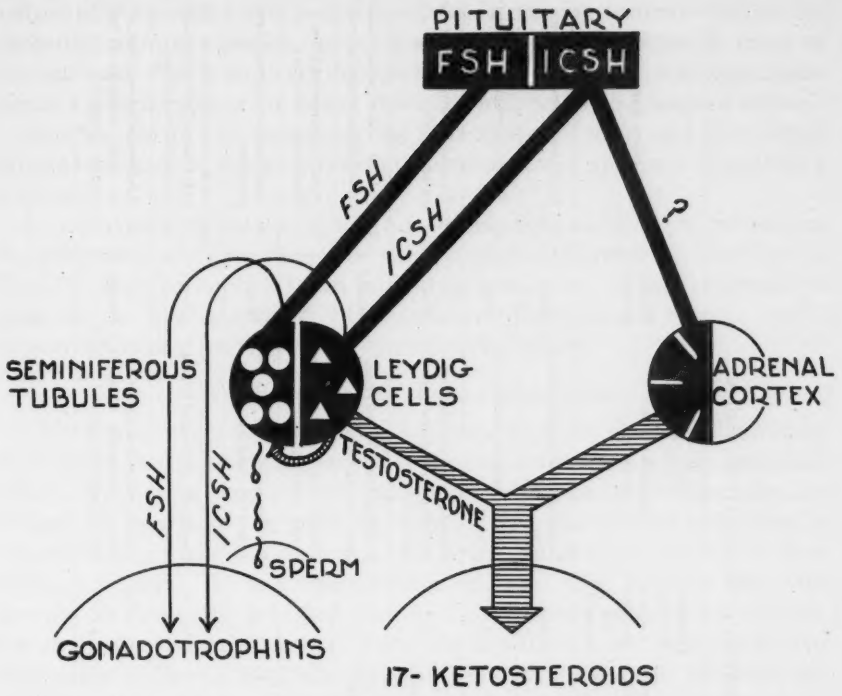

FIG. 1. PHYSIOLOGIC CONTROL OF THE TESTIS

F.S.H. refers to the follicle-stimulating hormone, which has a gametogenic function in males and females. It stimulates the germinal elements of the testis, promoting spermatogenesis in the seminiferous tubules (represented by circles). Note that testosterone plays a role in the maintenance of the seminiferous tubules.

I.C.S.H. refers to the interstitial-cell-stimulating hormone which stimulates the Leydig cells (represented by triangles) to produce testosterone. Formerly I.C.S.H. was known as luteinizing hormone (L.H.).

Together these two fractions constitute the *gonadotropic fraction*. In human urine the resultant action of F.S.H. plus I.C.S.H. is determined biologically.

17-Ketosteroids are hormones or their metabolites found in urine; approximately $\frac{3}{8}$ is derived from the testes and $\frac{5}{8}$ is derived from the adrenals. The term "17-keto" refers to the ketone (=0) attached to carbon atom number 17 of the steroid molecule.

Normal sperm count, morphology and motility indicate the entire system is functionally intact.

ure leading to testicular failure. Since the type and length of treatment depend upon this differentiation, it is important to distinguish between them.

Differentiation can be accomplished by either of two means: 1) favorable response to a simple therapeutic test employing injections of chorionic gonadotropic hormone (*see* next section); or 2) by determining the urinary

TABLE 1. CLASSIFICATION OF MALE HYPOGONADISM

Time of onset of hypogonadism (from patient's history and physical examination)	A. Gonadotropin titer determined by urinary assay B. *Response to chorionic gonadotropin*	Failure of other pituitary tropic hormones	Skeletal development	Gynecomastia	Testicular development, grossly. (++++ normal)	Testicular biopsy (microscopic)	Sexual potency	Definitive diagnosis
Before or during puberty	A. Low	Yes	Dwarfism	None	++	Infantile tubules and Leydig cells	Poor	(1) *Panhypopituitary dwarfism*
	B. *Positive response*	No	Eunuchoidal	None	++	Infantile tubules and Leydig cells	Poor	(2) *Hypogonadotropic eunuchoidism*
	A. High	No	Eunuchoidal	None to marked	0	Absent or very atrophic testes (Wolffian duct derivatives in scrotum)	Poor	(3) *Prepuberal noncastrate eunuchism*
	B. *Negative response*	No	Normal or eunuchoidal	None to marked	+	Hyalinized tubules and clumping of Leydig cells	Normal	(4) *Puberal seminiferous tubule failure* (Klinefelter syndrome)
After attaining sexual maturity	A. Low	Yes	Normal	None	+++	Tubules and Leydig cells returned to infantile state	Poor	(1a) *Adult panhypopituitarism* (Simmonds' cachexia)
	B. *Positive response*	No	Normal	None	+++	Tubules and Leydig cells returned to infantile state	Poor	(2a) *Adult hypogonadotropic hypogonadism*
	A. High	No	Normal	None	++++	Absence, disorganization or atrophy of tubules and Leydig cells	Poor	(3a) *Adult hypergonadotropic hypogonadism* (male climacteric or surgical castration)
	B. *Negative response*	No	Normal	None	+++ to ++++	Tubules reduced in size or hyalinized. Sloughing of germ cells. Leydig cells normal	Normal	(4a) *Adult seminiferous tubule failure* (most instances of irreversible sterility)

output of the gonadotropic hormones (2, 3). In primary testicular failure the output of pituitary gonadotropins is several times higher than in urines of normal men. When pituitary failure is responsible for the hypogonadism, urinary gonadotropins are either absent or well below the range of normal.

Another aid in distinguishing the four types of adult and prepuberal failure is a study of the variations in the microscopic anatomy of testicular biopsies.

By using each of the means mentioned, the eight distinct syndromes can be differentiated. This "key" to the hypogonadal states, as outlined in Table 1, may be applied to an individual patient in whom the tentative diagnosis is "hypogonadism." The definitive diagnosis can then be made. It also serves as a preview of the discussion to follow.

Therapeutic test with chorionic gonadotropin

This therapeutic test constitutes a pivotal point in the classification as well as in subsequent management of the patient suffering from hypogonadism. Favorable response to injection of chorionic gonadotropin as judged by growth of the genitalia signifies that the patient is lacking in gonadotropins since the patients with hypergonadotropic hypogonadism will not respond. As is amplified later, patients that respond may frequently be completely restored to normal by a course of chorionic gonadotropin therapy. In distinct contrast, the injudicious use of testosterone may cause sufficient testicular and pituitary suppression to preclude the possibility of subsequent stimulation of the testis. This undesirable possibility emphasizes the importance of proper classification and treatment.

The therapeutic test consists of the administration of 750 international units of chorionic gonadotropin intramuscularly *twice* daily for three weeks. If a response is elicited, the patient has hypogonadotropic hypogonadism and should be treated as outlined under this category. If no response is elicited and the patient is definitely hypogonadal, it can be safely assumed that the patient belongs to the hypergonadotropic category and that the primary site of involvement is the testis. Such a patient may be given substitutional therapy with testosterone, as outlined for the group of prepuberal noncastrated eunuchs.

The subsequent response of the patient bears out the findings obtained by the therapeutic test with chorionic gonadotropin. By actual assay of urinary gonadotropins a direct correlation is established. (In 100 per cent of the patients that responded favorably to the test, low urinary gonadotropic titers were found in the preliminary control period.) Additional confirmation is obtained from the microscopic anatomy of the testicular biopsies which show failure of stimulation of the Leydig cells and tubules, presumably because of the lack of gonadotropins. Conversely a positive corre-

lation is established between failure to respond to the test, high titers of urinary gonadotropins and biopsy evidence that the testes are absent or in such a state of damage that response to stimulation cannot be expected.

Classification into syndromes will follow the numbering system used in the key.

THE HYPOGONADOTROPIC SYNDROMES

FAILURE OF ALL FUNCTIONS OF THE ANTERIOR PITUITARY

1) **Panhypopituitary dwarfism.** Although this syndrome is rare, it is easily recognized by the short stature associated with lack of pituitary stimulation (a) to the thyroid gland, leading to hypothyroidism or myxedema; (b) to the gonads, leading to characteristic sexual infantilism; and (c) to the adrenal cortex, leading to an Addisonian-like picture.

1a) **Adult panhypopituitarism** (Simmonds' cachexia) is similarly rare and easily recognized by the failure of the thyroid, gonads and adrenals. It is often indistinguishable from the functional type of panhypopituitarism (anorexia nervosa) in both its clinical and laboratory manifestations.

A therapeutic test with chorionic gonadotropin elicits a positive response in both the prepuberal and adult types. Further, the urinary gonadotropin titers are low or absent, and testicular biopsies indicate the lack of pituitary stimulation. Evidence of insufficiency of the other tropic hormones distinguishes panhypopituitarism from the other hypogonadotropic syndromes.

Ideal therapy would consist of administering the various tropic fractions which are lacking, for example, growth, thyrotropic, adrenocorticotropic, follicle-stimulating, and interstitial-cell-stimulating hormones. Since these are not yet commercially available, administration of desiccated thyroid, adrenal cortical extract and the sex hormones is often resorted to with variable success.

FAILURE OF PITUITARY GONADOTROPIC SECRETION ONLY

2) **Hypogonadotropic eunuchoidism** superficially resembles other forms of hypogonadism in which the individual fails to undergo puberty. It is distinguished from panhypopituitarism in that the individual is tall rather than dwarfed and there is no evidence of deficiency of other pituitary hormones. The clinical features shared with other types of eunuchoidism (the prepuberal noncastrated type and the eunuchoidal type of seminiferous tubule failure) are: tall eunuchoidal skeletal structure (the span is two or more inches greater than the height, and the measurement from soles to pubic symphysis is one or more inches greater than the measurement from pubic symphysis to the vertex), delay in epiphyseal closure, poor development of paranasal sinuses and larynx, high pitched voice, subnormal de-

velopment of the male hair pattern, lack of recession of scalp hair line, poor muscular development and endurance, and sexual infantilism.

The following clinical features help to delineate hypogonadotropic eunuchoidism (Fig. 2) from other types of eunuchoidism: (a) more "progeria-like" wrinkling of the skin of the face; (b) although pubic, axillary

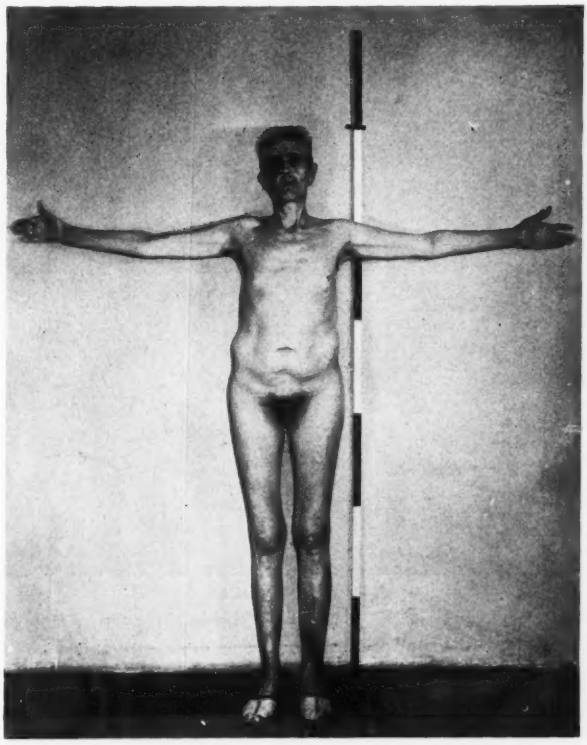

FIG. 2. Hypogonadotropic eunuchoidism in an untreated patient 51 years of age. Height, 70.5 in.; span, 73.3 in.; soles to pubic symphysis, 39.5 in.; pubic symphysis to vertex, 31 in. Roentgenograms revealed hyperostosis frontalis interna.

and extremity hair is decidedly less than in sexually normal males, more is present than in prepuberal noncastrated eunuchs. This may be correlated with (c) the level of excretion of 17-ketosteroids, which falls at or below the lower limits of normal but is higher than in the noncastrated eunuch. (d) Testes are always present but are smaller than normal, whereas the noncastrated eunuchs have none and patients with seminiferous tubule failure have very firm atrophic testes. (e) Mammary glands remain unde-

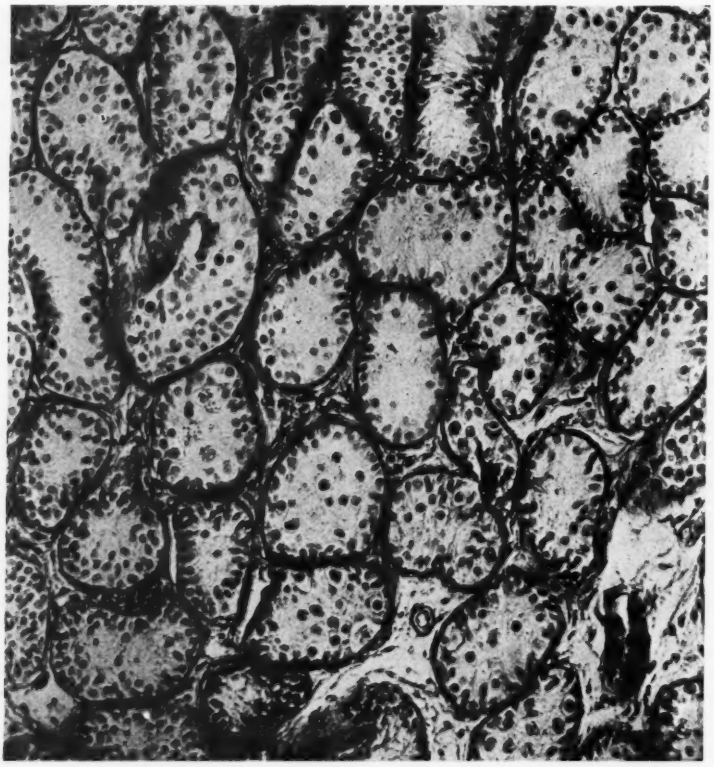

FIG. 3. Testicular biopsy (×175) from a patient 26 years of age with untreated hypogonadotropic eunuchoidism. Note presence of mesenchymal cells and absence of Leydig cells in the interstitial spaces, the small caliber of the seminiferous tubules and the absence of spermatogenesis beyond the spermatocyte stage. This biopsy reveals a suitable substrate, potentially capable of being stimulated.

veloped as in normal males, whereas in the other two syndromes there may be either gross or microscopic (biopsy) evidence of mammary stimulation.

The diagnosis is suggested by the presence of the findings described above, and established by:

1. A positive response to the administration of chorionic gonadotropin in adequate amounts.
2. Urinary gonadotropin titers below normal (or absent).
3. Testicular biopsies, revealing the presence of Leydig cells and some elements of the germinal series in an undeveloped state. These biopsies (Fig. 3) resemble testes seen in prepuberal boys and are somewhat similar to those of hypophysectomized animals.

Therapeutic program suggested for treatment of hypogonadotropic eunuchoidism: It is evident from the gonadotropin titers and testicular biopsies that the physiologic defect responsible for this syndrome is a lack of both interstitial-cell-stimulating hormone (I.C.S.H.) and follicle-stimulating hormone (F.S.H.). This suggests the use of these two hormones in any therapeutic program designed to stimulate the testes.

A. Administration of chorionic gonadotropin. In order to correct the hormonal deficiency of the testes a potent I.C.S.H. preparation capable of stimulating the Leydig cells is necessary. No purified I.C.S.H. of anterior pituitary origin is commercially available. Preparations of gonadotropin from the serum of pregnant mares and of chorionic gonadotropin from the urine from pregnant women, both have potent I.C.S.H. effects. However, the former has predominantly an F.S.H. effect whereas purified preparations of chorionic gonadotropin are regarded as free of F.S.H. effect. Since we have been interested in elucidating mechanisms of action throughout our studies we have elected to use those preparations which have the activity of a single hormone. In this instance chorionic gonadotropin was the substance chosen. Synonyms for this substance are: prolan, pregnancy urine extract, placental gonadotropin and anterior pituitary-like hormone. Chorionic gonadotropic hormone is presumably secreted by the chorionic cells of human placenta and is derived commercially from the urine of pregnant women. It is a complex protein substance with an unknown chemical formula and it has not been synthesized. It is standardized in international units.

The commercial preparations, currently available on the market, which were used in this study include: "Pranturon" (Schering), "Korotrin" (Winthrop), "Chorionic gonadotropin" (Upjohn), "A.P.L." (Ayerst, McKenna and Harrison), and "Antuitrin-S" (Parke, Davis & Co.).[1] All proved to be equally effective when employed under similar conditions. Others currently available include "Follutein" (Squibb), "Chorionic gonadotropin" (Armour), "Chorionic gonadotropin " (Sharpe and Dohme), and "Pregnyl" (Roche-Organon).

In our experience the most efficient mode of administration is as follows: inject 750 international units intramuscularly twice daily for at least four to six weeks. The dose may then be reduced by one-half and continued an additional two months. Allow a rest period of from three to six months. At the end of this period it must be ascertained whether the developmental changes effected by the homone have been maintained or have regressed,

[1] We are especially grateful to Dr. Gifford Upjohn of the Upjohn Company, Kalamazoo, Michigan, for providing us with well over one million units, and Dr. Edward Henderson of the Schering Corporation, Mr. Carr of Winthrop, and Dr. Murray Scott of Ayerst, McKenna and Harrison for the generous supplies of chorionic gonadotropin they provided.

or whether there has been further development subsequent to the cessation of therapy. The last situation indicates spontaneous improvement and in this event improvement may continue without any further treatment. In

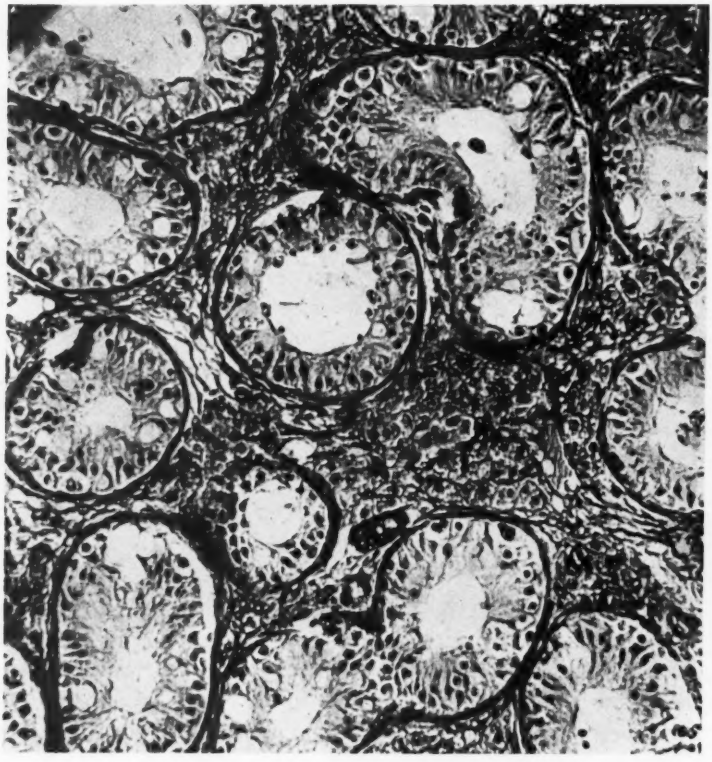

FIG. 4. Testicular biopsy (×175). A case of hypogonadotropic eunuchoidism after treatment with chorionic gonadotropin in a dose of 1500 I.U. 5 times weekly for four months. Note appearance of Leydig cells in the interstitial spaces. These were producing androgen, as may be seen from Figure 5, which shows the genitalia before and after the four-month period. Note larger tubules (due to androgen stimulation) and lack of spermatogenesis beyond spermatocyte stage.

the other instances further therapy is necessary. The usual procedure is to alternate three-month periods of treatment with three-month periods of rest. A surprisingly large proportion of the cases of hypogonadotropic eunuchoidism will maintain their improved status or actually continue to develop toward normal without further therapy after six to eighteen

months on this program. One plausible explanation is that a trigger mechanism, which had failed to be set off at the time of the normally expected puberty, has been set off by the administration of chorionic gonadotropin. Thus the previously underactive pituitary gland, in some unexplained manner, has been stimulated to secrete gonadotropins. The process, having once been initiated, continues spontaneously.

Testicular biopsies taken on the same individual before and after

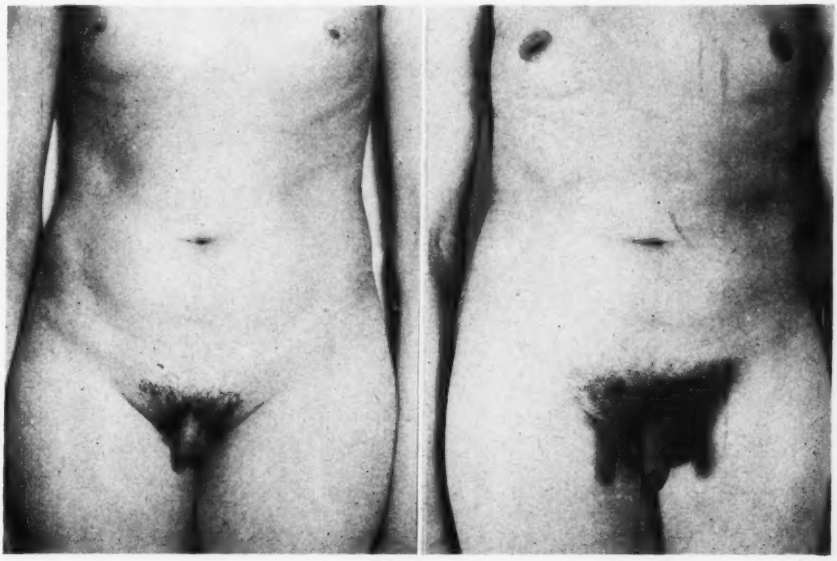

FIG. 5. Hypogonadotropic eunuchoidism in a man 26 years of age, before and after four months of chorionic gonadotropin therapy. The testicular biopsies shown in Figures 4 and 6 are from this patient.

chorionic gonadotropic therapy show marked stimulation of the Leydig cells and increase in size of the seminiferous tubules but no increase in spermatogenesis (Figs. 3 and 4). This indicates that chorionic gonadotropic hormone stimulates Leydig cell growth and secretion.

This therapy has been uniformly successful in all cases. This success can be ascribed to three important factors: 1) establishment of the proper pathologic-physiologic diagnosis; 2) use of adequate amounts of the hormone; and 3) administration of it at frequent intervals. The use of large amounts of hormone at frequent intervals seems complicated and expensive. The gratifying results accomplished over a short period (Fig. 5) and the

lack of necessity for continued treatment in most cases, actually makes this method less expensive than the use of inadequate doses at infrequent intervals over longer periods of time.

FIG. 6. Testicular biopsy (×175). The same case of hypogonadotropic eunuchoidism shown in Figures 4 and 5, after adding follicle-stimulating hormone to the therapy (one-half cc. of F.S.H., 519, prepared by Dr. H. McShan of the University of Wisconsin, was administered intramuscularly 5 times weekly for three months, omitted for six weeks, then administered again in a dose of 1 cc. 5 times weekly for two months, at which time spermatozoa were noted in the seminal fluid for the first time and a biopsy specimen was procured). Note that all stages of spermatogenesis are present and the tubules are larger than in Figure 4.

B. Administration of follicle-stimulating hormone. Chorionic gonadotropic hormone therapy corrects only the hormonal but not the germinal deficiency of the hypogonadotropic eunuchoid. We have been fortunate in having a purified follicle-stimulating hormone prepared by and made

available through the courtesy of Dr. H. McShan of the University of Wisconsin, which has been added to the therapeutic regimen of some patients following their response to chorionic gonadotropin. Testicular biopsies taken before adding F.S.H. revealed no spermatogenesis, and the seminal fluid contained no spermatozoa. F.S.H. was given once daily intramuscularly in large doses and biopsies were obtained from two to three months later. Testicular biopsies (Fig. 6) and examination of seminal fluid both indicated that F.S.H. administration had stimulated spermatogenesis.

Unfortunately, so far as we know, no purified or highly potent F.S.H. is as yet available commercially. However, there are mixtures of F.S.H. and I.C.S.H. derived from anterior pituitary sources on the market which may prove to be of benefit. We have employed "Preloban Niphanoid" (Winthrop) with some success. Since no uniform standards are available for the mixture no specific recommendations as to dosage can be made.

2a) **Adult hypogonadotropic hypogonadism.** No skeletal changes are to be expected and, in general, masculine characteristics are retained. Our single example of this condition exhibited slight regression of facial and bodily hair growth, sexual impotence, and symptoms associated with the male climacteric. Administration of chorionic gonadotropin reversed the symptom complex.

THE HYPERGONADOTROPIC SYNDROMES

FAILURE OF LEYDIG-CELL FUNCTION

In this type of primary testicular failure, as well as in the syndromes where the seminiferous tubules are mainly involved, the chorionic gonadotropins elicit no response, titers of urinary gonadotropins are higher than normal, and biopsies fail to reveal testicular tissue capable of stimulation. The four syndromes to be discussed here as examples of primary testicular failure are therefore also to be called the *hypergonadotropic syndromes.*

3) **Prepuberal noncastrated eunuchs**[2] (Fig. 7) are eunuchoidal individuals who either failed to develop testes (testicular agenesis) or whose testes underwent complete atrophy before the age of puberty was reached (5). Surgical castrates whose orchidectomy antedated puberty may be included, since, according to Wagenseil (6), they have the same clinical features and similarly elevated gonadotropin titers (7).

In addition to having the features common to all types of eunuchoidism (listed in part under hypogonadotropic eunuchoidism) the prepuberal noncastrated eunuchs have the following distinguishing features: (a) diminution of scrotal contents, often leading to the incorrect diagnosis of

[2] Also referred to as functional prepuberal castrates.

abdominal testes; (b) the least pubic and axillary hair encountered in any of the eunuchoidal syndromes; (c) very low 17-ketosteroid excretion; (d) gynecomastia which is usually obvious on physical examination but occasionally discovered only by a mammary biopsy; (e) no response to the administration of chorionic gonadotropins; (f) high titers of urinary gonadotropins. Biopsies of the scrotal contents reveal the presence of

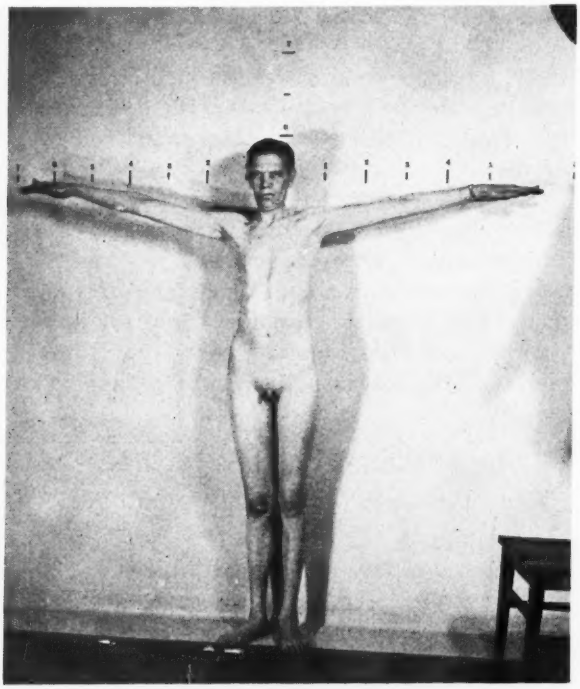

FIG. 7. Prepuberal noncastrated eunuch 32 years of age.

Wolffian duct derivatives, but absence of functional testes (Fig. 8). Remnants of atrophic testes are occasionally discovered.

Therapy must necessarily be substitutional in nature. Twenty-five mg. of testosterone propionate[3] administered five times weekly intramuscularly is satisfactory. Implantation of six to eight pellets of testosterone weighing

[3] Testosterone propionate (Oreton) and testosterone pellets were kindly provided by the Schering Corporation, Bloomfield, New Jersey, through the courtesy of Mr. George Straayer and Dr. Edward Henderson.

75 mg. each is more convenient and gives equivalent results. Implantation needs to be repeated only every six or eight months.

3a) **Adult hypergonadotropic hypogonadism.** As in other instances where gonadal failure develops after maturity is reached, the normal male habitus is largely retained. Only after years of testicular deficiency does one note any regression of hair growth or diminution in genital size. The chief complaints of this group of patients are either sexual impotence or symptoms

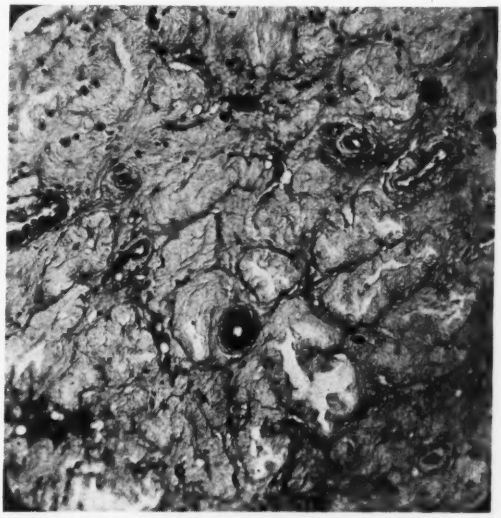

FIG. 8. Biopsy of scrotal contents (×175) in a prepuberal noncastrated eunuch 52 years of age. Note remnants of seminiferous tubules. This biopsy fails to reveal a substrate capable of being stimulated (reproduced from Heller, C. G.; Nelson, W. O., and Roth, A. A.: *J. Clin. Endocrinol.* **3**: 573, 1943).

of the male climacteric (8). It is interesting to note that climacteric symptoms arise only in individuals who at one time have had a fair degree of Leydig cell function, suggesting that the symptoms are related to withdrawal of the sex hormones. Climacteric symptoms may arise as a consequence of gonadal failure secondary to pituitary failure as well.

To substantiate the diagnosis of adult hypergonadotropic hypogonadism as the factor responsible for impotence or climacteric symptoms, one needs to find (a) high titers of urinary gonadotropins, or (b) evidence of failing Leydig cell function in a biopsy specimen, or (c) lack of response to chorionic gonadotropin plus a definite response to testosterone (8) administered in adequate amounts such as 25 mg. five to seven times weekly intramuscu-

larly for two weeks. A positive response indicates that testicular failure is present whereas a negative response suggests psychogenic impotence or psychoneurosis. In some instances the etiology of the testicular failure is apparent, for example, bilateral orchitis, trauma, surgical castration, or interference with testicular blood supply following herniorrhaphy, In most instances, however, no etiologic factor can be elicited.

Treatment is as outlined for prepuberal noncastrated eunuchs.

SEMINIFEROUS TUBULE FAILURE

4) **Puberal seminiferous tubule failure** (9) is the most common form of gonadal failure and yet is least often recognized. The primary defect con-

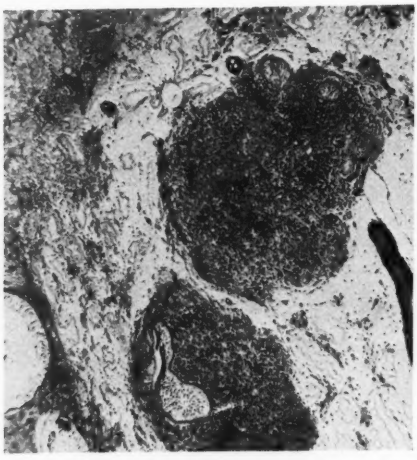

FIG. 9. Testicular biopsy (×80). Puberal seminiferous tubule failure. Note hyalinized seminiferous tubules, occasional tubule devoid of cells of the germinal series and containing Sertoli cells only, and aggregation of Leydig cells of small type.

sists of disappearance of germinal cells and hyalinization of the seminiferous tubules, but this rarely exists without concomitant involvement of the Leydig cells although to a much lesser degree. If a patient is seen relatively early in the course of the disease, Leydig cell function may be so little disturbed as not to be detectable clinically. The main distinguishing features common to all cases of prepuberal hyalinization of the tubules are: (a) azoospermia; ejaculation is usually normal but the seminal fluid is devoid of spermatozoa; (b) very small testes in a normally developed scrotum —testes are unusually firm and range in size from that of a pea to that of an average lima bean, although in rare instances, the testes are almost of

normal size; (c) there is a negative response to chorionic gonadotropin and urinary gonadotropins are elevated to the levels found in castrates; (d) testicular biopsy examination (10) reveals hyalinization of the tubules and aggregation of Leydig cells (Fig. 9) with an apparent increase in their total number (11).

Three clinical subtypes (9) are recognizable, depending apparently upon

FIG. 10. Puberal seminiferous tubule failure—noneunuchoidal type.

the degree of involvement of the androgen-secreting cells of Leydig. These clinical types may be divided according to their appearance into: 1) the noneunuchoidal group[4] (Fig. 10) in which the patients invariably exhibit gross gynecomastia; 2) the moderately eunuchoidal group (Fig. 11) in which there is slight gynecomastia and a few eunuchoidal features; and 3) the eunuchoidal group (Fig. 12) in which the patients exhibit the features of classical eunuchoidism but lack gross signs, although they may have microscopic evidence of gynecomastia. It should be remembered that al-

[4] "Noneunuchoidal" has been substituted for "normal," as suggested by Bettinger and Robinson (12).

though the degrees of clinical hypogonadism and of Leydig cell failure are variable, seminiferous tubule failure is invariable; and members of all three groups have the findings associated with hyalinized tubules. It is presumed that the quality of the Leydig cells is poor in all cases since all of the patients we have observed developed symptoms of the male climacteric by the time they reached the age of 25 years.

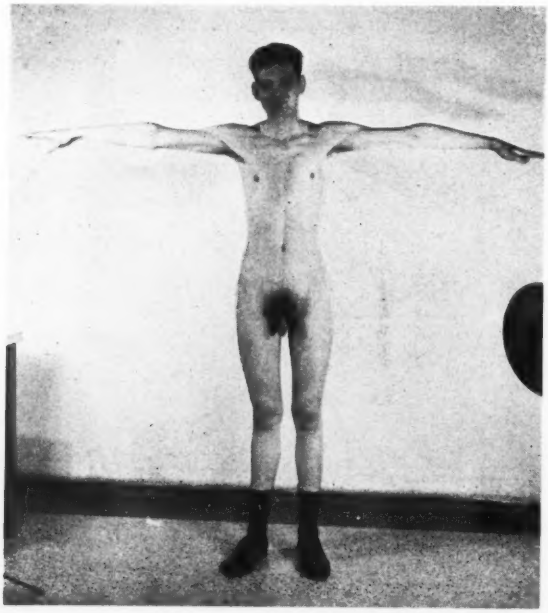

FIG. 11. Puberal seminiferous tubule failure—moderately eunuchoidal type. Note great similarity to normal male, but absence of facial and axillary hair, high-pitched voice, lima bean-sized testes, lack of recession of hair of forehead, and moderately eunuchoidal skeletal structure all aid in distinguishing from normal male.

We consider the defect in puberal seminiferous tubule failure to be of congenital origin. Reifenstein (13) has noted its occurrence in 9 members of the same family. The defect makes its appearance at the time of puberty as judged by clinical history, physical examination and histologic findings in the testis. All patients exhibit some degree of androgen secretion at puberty. In the noneunuchoidal group onset of the gynecomastia and atrophy of the testes may be traced to the time of puberty. The seminiferous tubules and Leydig cells both show evidence of puberal stimulation before the onset of failure.

Therapy. Neither the gynecomastia nor the sterility (azoospermia) can be corrected hormonally. However, by instituting substitutional therapy with testosterone, as previously outlined, most gratifying increases in muscular strength and endurance, improvement in confidence, self esteem and reversal of neurotic tendencies result. Improvement in sexual function results as well (14).

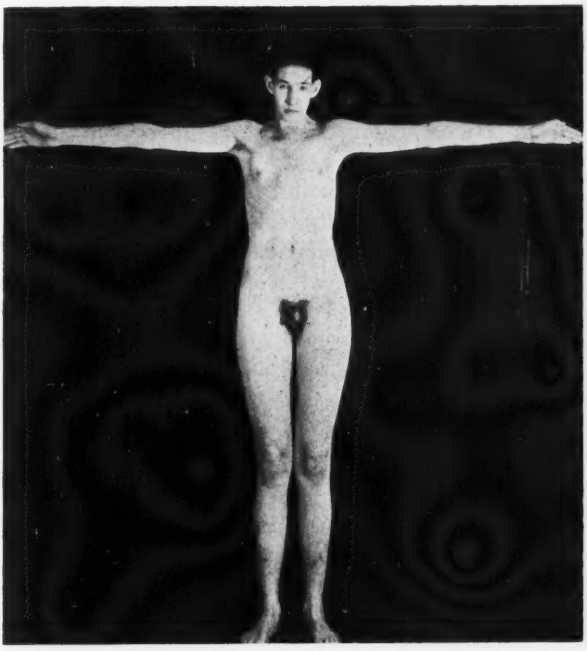

FIG. 12. Puberal seminiferous tubule failure—eunuchoidal type. Courtesy of Dr. D. R. Sparkman, Seattle.

4a) **Adult seminiferous tubule failure,** is usually discovered only in the course of an evaluation of instances of sterility. No clinical signs or symptoms are apparent. Seminal fluid examination reveals azoospermia or oligospermia. The testes are usually of normal size and consistency. If failure is complete, urinary gonadotropin levels are markedly elevated and testicular biopsies demonstrate either empty seminiferous tubules in which no elements of the germinal series are seen or hyalinization of the tubules (15). No effective treatment has been found.

DISCUSSION

Albright et al. (16) first proposed a scheme for the classification of hypogonadism based upon identifying the physiologic defect involved. Subsequently a number of syndromes have been described which either confirmed the existence of certain of the syndromes postulated by them or represented additional types of hypogonadism (4, 5, 6, 7, 8, 9, 10, 14). These have been taken into account and included in the present classification.

Several other so-called "syndromes" have been taken into account and have been eliminated from the classification. These include:

Prepuberal hypogonadism. Such a syndrome cannot exist (even in the absence of testes) since all children are hypogonadal before the onset of puberty. Thus variations in stature, genitalia, or fat cannot be ascribed to hypogonadism.

The diagnosis of hypogonadism during the teens is difficult to make, since the onset of puberty may vary from age 8 to age 22 in perfectly normal children, depending largely upon whether they are early or late maturing varieties. Only the hypergonadotropic syndromes can be positively identified during this period with the aid of testicular biopsies, gonadotropin assays or a therapeutic test with chorionic gonadotropin.

Frölich's disease is used to designate lesions of the hypothalamus. Occasionally the involvement of the hypothalamus is due to a pituitary growth. In this rare instance both hormonal and hypothalamic manifestations could be expected. Although hypothalamic lesions may possibly alter anterior pituitary function, they are encountered so infrequently that there should be great hesitancy in making this diagnosis.

Adiposogenital dystrophy and other such anthropometric designations are meaningless anachronisms of a previous era.

Polyglandular insufficiency is an unnecessary term since, if more than one gland has failed, each failure can be identified.

The reader is referred to the review by Werner (17) for details concerning etiology and for a more classical approach to the problem of classification of hypogonadism. For other discussion involving a physiologic approach see references 18, 19, 20 and 21.

SUMMARY

A simple "key" has been devised to aid in establishing to which of eight definitive diagnostic categories a given hypogonadal male patient belongs. Each of the eight syndromes is briefly described and treatment is suggested for each.

The age at onset of the defect (before, at, or after puberty) and its exact location (indicating which function of the pituitary or testis is involved) determines the diagnosis as well as the treatment.

In all instances of hypogonadism there are marked deviations from normal in the output of urinary gonadotropins. The groups with testicular failure invariably show excretions higher than normal and therefore are designated as the hypergonadotropic syndromes. Those with pituitary failure (and secondary testicular failure) invariably show subnormal excretions and are therefore designated as the hypogonadotropic syndromes.

The injection of chorionic gonadotropin in adequate amounts is stressed as an aid in making this important differentiation, in lieu of the gonadotropin assays on urines.

The role of testicular biopsies as diagnostic aids is discussed.

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MALE PSEUDOHERMAPHRODITISM*

PROVED BY SURGICAL EXPLORATION AND MICROSCOPIC EXAMINATION

A CASE REPORT WITH SPECULATIONS CONCERNING PATHOGENESIS

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WHEN an unusual case presents itself and challenges the validity of current concepts for its explanation, one should be prepared for surprises. The following case found us totally unprepared for the answer.

CASE RECORD

J. W., a 19-year-old girl of Scandinavian-Scotch-Irish ancestry, was referred for study because she had never menstruated. She was the middle one of three sisters in a family in which the only suggestion of endocrine abnormality was the occurrence of unusually tall women (6 ft.) on the maternal side.

Born at term of an uneventful pregnancy, the patient had been a healthy, apparently normal girl who had had the usual quota of uncomplicated childhood diseases. The first sign of puberty appeared at 15 years when her breasts began to develop. Two years later she had attained a height of 69 inches and required a size 34 brassiere. The fact that she had not menstruated did not seem significant as her mother's menarche did not occur until her seventeenth year and the elder sister's in her sixteenth year. When at 18 years of age the menses had not appeared, the patient sought medical aid and consulted one of us (A. F. M.). Pelvic examination revealed a rudimentary vagina and the absence of uterus and cervix. Ethinyl estradiol, 0.1 mg. daily for two weeks each month, was prescribed. This therapy, continued for four months, resulted only in increased size of the breasts. Further investigation was interrupted when the patient developed a pleural effusion with fever, cough and night sweats. A diagnosis of tuberculous pleurisy necessitated six months' hospitalization at the San Fran-

Received for publication January 16, 1948.

* Presented in brief under the title of "Bilateral Arrhenoblastoma without Masculinization" at the 29th Annual Meeting of the Association for the Study of Internal Secretions, June 6, 1947, Atlantic City, New Jersey.

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cisco Tuberculosis Hospital during which time hormone treatment was suspended. In February, 1946, she was discharged from the hospital as cured, and soon after was referred for further study of her endocrine condition.

When seen on April 30, 1946, the patient appeared to be a tall, athlet-

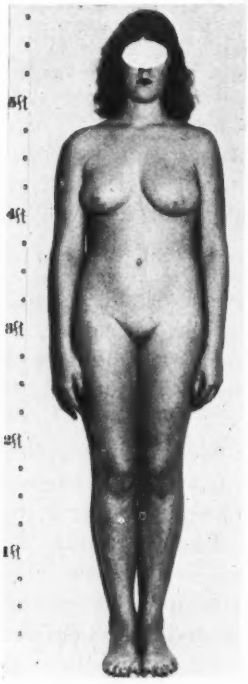

FIG. 1. J. W., aged 19. Note tall eunuchoid build, absence of pubic hair, large, well-developed breasts.

ically built, well nourished girl with relatively long arms and legs, a prominent lower jaw and rather large breasts (Fig. 1). Her voice was pleasantly feminine though of low pitch. The blood pressure was 120/60. Her measurements were as follows:

Weight	159 lbs.	(72.3 Kg.)
Height	70½ inches	(79 cm.)
Span	73½ inches	(86.7 cm.)
Vertex to pubis	33½ inches	(85.1 cm.)
Pubis to floor	37 inches	(94.1 cm.)
Ratio upper/lower	0.90	—

The skin was soft, smooth, and hairless. Pubic and axillary hair was absent but a slight trace of vulval hair was discernible. The labia majora and minora were normally developed but small. A perforate hymen spanned the vagina which ended blindly at a depth of 2.5 cm. The urethra occupied its usual position but the clitoris was represented by only a dimple. On palpation no pelvic organs could be felt. The other noteworthy positive physical findings were: a narrow mandible with crowded lower teeth; a high arched palate; a maldevelopment of the ear lobule on the left; slight asymmetry of the chest with dullness and absent breath sounds over the right side posteriorly; large full breasts with prominent areolae but small poorly developed nipples.

Laboratory data: Routine blood count, urinalysis, and blood serology were negative. Urinary gonadotropin assay (F.S.H.)[1] showed at least 96 m.u./24 hours but not as much as 192 m.u. (normal values: 13 to 50 m.u.). Vaginal smears stained with Shorr's trichrome stain showed fully cornified epithelial cells indicating estrogen effect.

X-ray findings: Roentgenograms of the skull demonstrated the extreme narrowing of the lower jaw but were otherwise normal. Those of the skeleton revealed a bone age of 19 to 20 years with no further potential for linear growth remaining. No osteoporosis or abnormal calcifications were noted.

Preoperative consideration: What were the diagnostic possibilities? Here was a tall 19-year-old girl with eunuchoid proportions, poorly developed external genitalia, absent uterus and cervix, moderately high urinary F.S.H. excretion but with large breasts. To explain the last, it seemed reasonable to suppose that some functioning ovarian tissue must be present despite the fact that the adnexa were nonpalpable. Since the patient was contemplating matrimony and wished a plastic operation performed on the vagina, it was decided first to determine her gonadal status either by peritoneoscopy or by pelvic laparotomy. The latter course was chosen because of previous unreliable results with peritoneoscopy in our hands.

Surgical exploration, December 16, 1946: Under sodium pentothal and cyclopropane anesthesia, the abdomen was opened through a midline incision. Exposure of the pelvis (Fig. 2) revealed no structures between the rectum and the bladder other than a fold of peritoneum which formed a shelf-like projection. Laterally and quite high in the pelvis were two shiny grayish-white, ovoid bodies, one on each side, measuring about $2.5 \times 1.5 \times 1.5$ cm. Contiguous with the distal ends of these bodies were two fleshy, pyriform structures resembling the unfused horns of a uterus. The thickened fold of peritoneum stretching from these structures to behind the

[1] Method of Klinefelter, Albright and Griswold (1) (slightly modified).

bladder suggested round ligaments. Adjacent laterally to the rudimentary gonads were apparently normal tubes with fimbriated ends adherent to the upper poles. Folds of peritoneum corresponding to the uterosacral ligaments were well developed.

Although the gonadal structures had the innocent appearance of aplastic nonfunctioning ovaries, a biopsy seemed indicated. As the scalpel cut through the thick white capsule, it revealed unsuspected dark brown tissue (Fig. 3). Frozen sections showed the tissue to be composed entirely of

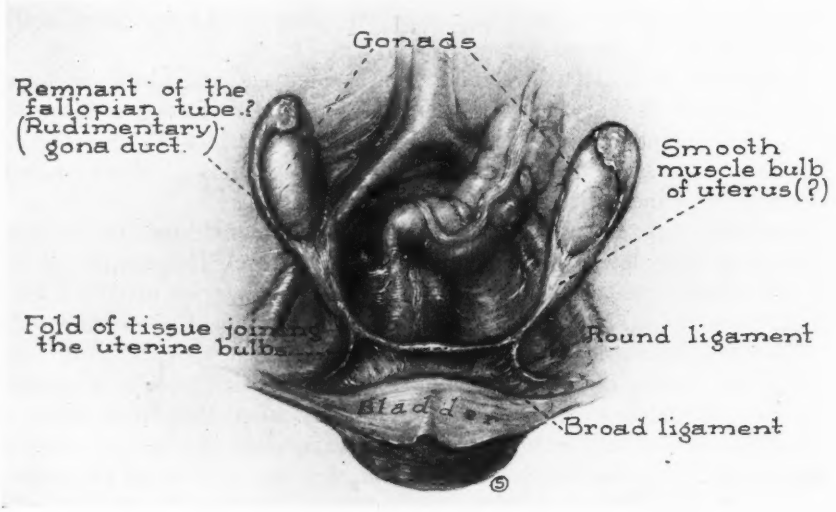

FIG. 2. Drawing of pelvic organs as seen at surgical exploration.

seminiferous tubules identical with the picture of Pick's "adenoma tubulare testiculare." A tentative diagnosis of arrhenoblastoma was made. The second "gonad" on section displayed the same gross appearance as the first. Both gonads with their respective tubes and the left rudimentary uterine horn were removed as well as the appendix. Numerous congenital bands were found around the appendix and the ileocecal valve. Exploration of the upper abdomen revealed a right adrenal which, through the peritoneum, seemed to be about the size of an almond. The left adrenal was somewhat smaller.

Subsequent course: 17-Ketosteroid excretion in the urine had not been determined prior to operation. A belated 24-hour specimen collected immediately following surgery assayed 7.2 mg./24 hours.[2] This is well within

[2] Method of Pincus (2).

the normal range. The postoperative course was uneventful. Six weeks later the patient reported that she felt well although she had lost about ten pounds in weight and was somewhat nervous. The only notable physical change other than a pallid appearance was that the breasts seemed smaller and flabbier. Vaginal smears showed atrophic cells and many leukocytes. Not until three and a half months postoperatively did the patient volunteer the information that she was having hot flashes and increased perspiration. Urinary gonadotropin assay at this time was positive

FIG. 3. Bisected right gonad. Note rudimentary fold suggesting gonaduct.

for 195 m.u./24 hours. Oral administration of ethinyl estradiol 0.05 mg. daily produced prompt relief of symptoms.

Psychologic aspects: Inquiry into the psychologic aspects of this case brought out the following information: The patient was of an affectionate nature and enjoyed manifestations of affection from the opposite sex. However, she had always felt herself to be different from other girls in a very indefinite sort of way. Whether this was due to her physical difference or to an actual psychologic difference is impossible to say. Since the operation she is more than ever anxious for marriage and seems cheerful, happy and full of vitality.

Gross pathology: The material received consisted of two smooth, bluish white masses. One was from the right and the other from the left posterolateral pelvic wall, with elongated rounded folds attached to each mass. There was a separate mass from the left posterior pelvic wall and an appendix. The right bluish white mass was $2.7 \times 2 \times 1.5$ cm. On section the surface was lobulated, soft, and brown in color with a scattering of firmer pale yellow discrete nodules from 0.4 to 1.4 cm. in diameter (Fig. 4). The

left mass was 3×1.5×1.2 cm. On section, the surface was similar to that of the right mass except that only one discrete yellow nodule 0.5 cm. in

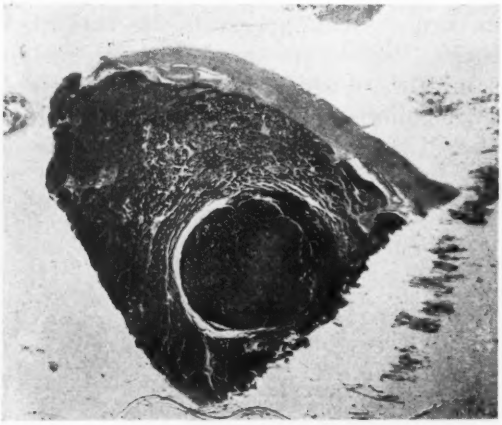

FIG. 4. Cross section of right gonad. ×10. Note thick tunica and discrete adenoma.

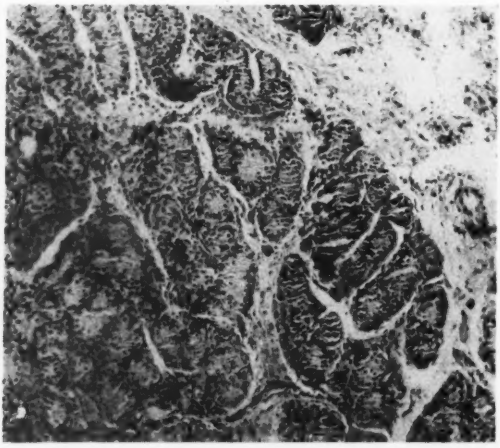

FIG. 5. Cross section of left gonad. ×120. Note small calibered tubules and islands and strands of interstitial cells.

diameter was apparent. The cylindrical structures were 2.5 cm. long and 0.5 cm. in diameter; a narrow longitudinal area was dissected but otherwise the structures were covered by peritoneum. The separate piece of tissue measured 2×2×1 cm.; one surface was white and glistening whereas

the opposite surface was dissected. On section the surface had a faintly striated pattern.

Microscopic pathology: The two bluish white masses were similar in structure (Fig. 5). Each was covered by a collagenous fibrous tissue capsule

FIG. 6. Cross section of left gonad. Note immature tubules, absence of spermatogenesis and islands of interstitial cells.

from 2 to 3 mm. thick. Narrow fibrous septa containing irregularly distributed groups of cells morphologically resembling Leydig cells divided the soft brown tissue into irregular lobules. This tissue was made up of cords which varied considerably in structure but in general resembled immature seminiferous tubules. The narrower cords had a central mass of basophilic, granular material and a single layer of peripheral round nuclei with loosely spaced chromatin granules. The centers of the wider cords were paler staining and contained more deeply staining radial strands and small, faintly basophilic ovoid bodies. In these cords the cell membranes were often indefinite, the cytoplasm pale staining, and the nuclear chromatin more distinctly granular. The nuclei were all uniform in size and none of the cells displayed the characteristics of spermatogonia or Sertoli cells[3]

[3] A portion of the tissue fixed in formalin was later sent to Dr. Warren O. Nelson of the Medical School of Iowa State University for additional study. His report corroborated the fact that the overwhelming majority of the tubular cells were relatively undifferentiated. However, by special staining technic he was able to identify occasional Sertoli cells.

(Fig. 6). There were no rete tubules. Sections at various levels of the folds which suggested gonaducts showed only fat covered by a thin layer of mesothelium. No epithelial structures were evident. Sections of the cephalic end of one of the rounded folds, however (Fig. 7), showed an indentation lined by long narrow plicae covered by ciliated high columnar epithelium. At the open end, a wider plica on one border resembled a fimbria. The wall was composed of fibrous tissue with irregularly distributed smooth muscle

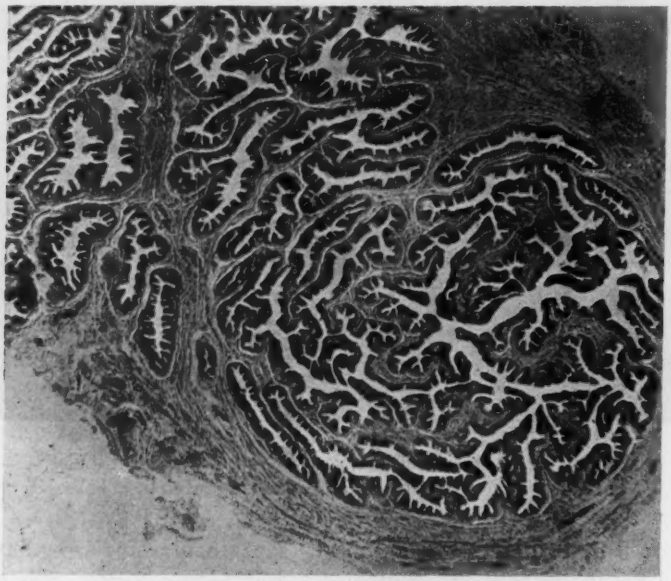

FIG. 7. Cross section of cranial portion of rudimentary tube. ×70.

bundles. The separate mass from a lower level was composed of interlacing bundles of smooth muscle fibers containing some nerve structures and sinusoids characteristic of myometrium (Fig. 8). No epithelial components were noted in any of the sections of this structure.

Pathologic diagnosis: 1) Fetal testes with adenomata, and hyperplasia of interstitial cells. 2) Wolffian agenesis. 3) Rudimentary Müllerian derivatives.

DISCUSSION

Although the preliminary diagnosis of adenoma tubulare testiculare of Pick (3) based on the microscopic picture was correct, the assumption that this represented a highly differentiated form of arrhenoblastoma of the

type described by Meyer (4) was in error. Careful search both grossly and microscopically failed to reveal any vestige of ovarian tissue. Obviously the diagnosis was neither arrhenoblastoma nor ovotestis. These gonads were immature, sterile, cryptorchid testes showing the typical adenomatous formation, small calibered tubules without spermatogenesis, and increased development of interstitial cells described over and over again in the literature (3, 5, 6, 7). This girl (?) then was an intersexed individual represent-

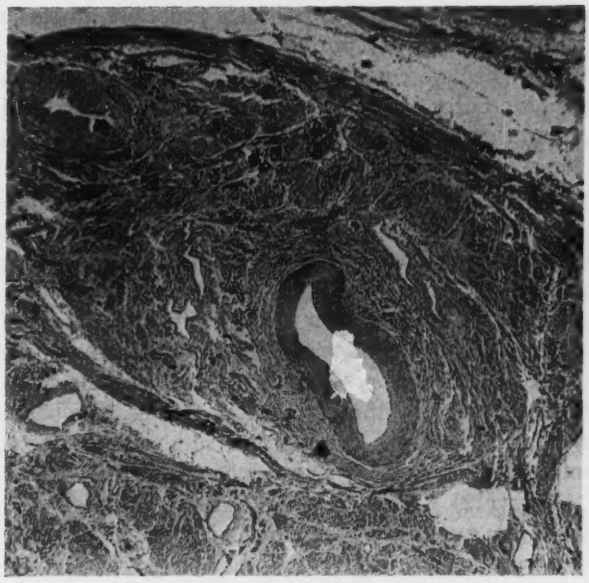

FIG. 8. Cross section from uterine anlage. ×70.

ing another instance of male pseudohermaphroditism with Müllerian derivatives and complete agenesis of the Wolffian system.

Incidence: Why did we fail to recognize the true situation at the time of operation? Pseudohermaphroditism is not such a rare condition. According to Young (7) the incidence is as high as 1 in 1000 individuals. The literature is full of descriptions of various types of intersexuality. Clinical recognition of these has depended for the most part on the presence of external genital anomalies. Surgical repair of hernias containing anomalous gonadal structures and laparotomies for intercurrent conditions have brought to light other instances but the condition has often remained unsuspected throughout life only to be revealed at necropsy. This is particularly true of the type of case described herein, exhibiting 1) completely

feminine habitus without any signs of masculinization, 2) amenorrhea accounted for by the absence of a normally developed uterus, and 3) testes in lieu of ovaries in the *intra-abdominal* position.

It is not the purpose of the authors to tabulate all the recorded cases of this kind. Suffice it to say that a review of hundreds of instances of pseudohermaphroditism in the available literature brought to light only 7 cases which fulfill the above criteria (5, 8, 9a, 9b, 9c, 10, 11). That the incidence is undoubtedly much greater than the above figure would indicate seems likely, as many such individuals probably go through life unsuspected, undetected and unreported.

Pathogenesis: When we come to a consideration of the pathogenesis of this condition, we enter into a field of pure speculation. Is it due to a genetic or chromosomal fault at conception or to some modifying environmental influence in early embryonic life? Although at the present time this question cannot be answered definitely for the human being, a brief review of some of our present concepts of the genetics and embryology of sex in correlation with the findings in this case may throw some light on this interesting problem.

From the genetic standpoint, the sex of a zygote is determined at fertilization by the chromosomal content of the fertilizing sperm. The mechanics is uncertain but it is generally accepted that the genes synthesize enzymes which control the differentiation of tissues. The balance between the autosomes and a single X chromosome results in a male embryo, two X chromosomes being necessary to produce a female. According to Goldschmidt's theory (12), this differentiation is quantitative rather than qualitative and any quantitative alteration in balance between X chromosomes and autosomes may give rise to various degrees of intersexuality. So much for the genetic factors. Progressing then from the conditions prevailing at conception, the next step is embryologic development. In the human being this is divided into three main stages: 1) the period culminating in the implantation of the blastocyst, or the first three weeks; 2) the embryonic period, from the beginning of the fourth week to the end of the eighth week, characterized by rapid growth and differentiation of tissues. It should be noted that during this period all the main systems and organs and the major features of the external body form are established; and 3) the fetal period from the ninth week to term characterized more by added increment of growth than by tissue differentiation (13).

Through the first seven weeks of gestation there is no discernible difference between the male and female embryo. Sexual differentiation commences at this time (17 mm.) and is usually complete by nine weeks (33 mm.). Development of the gonads and that of the gonaducts proceed independently of each other at this stage under genetic control (14). This is well illustrated by the perfect development of the Müllerian system in those

cases with absent or aplastic ovaries (15). Fusion of the Müllerian ducts occurs at eight weeks (25 mm.). This failed to occur in our patient. The gonad of the male embryo at 20 mm. shows beginning interstitial cell formation but the tubules are composed entirely of small undifferentiated testicular cells. Spermatogonia can be differentiated at 31 mm. (16). In our patient the interstitial cells were well developed but no spermatogonia were found. At eight weeks (25 mm.) the genital tubercle becomes bent caudally and can be recognized as the clitoris. In our case the clitoris failed to develop. Concerning the origin of the vagina there is some difference of opinion. Koff (17) claimed that approximately the lower one-fifth of the vagina is derived from the endoderm of the urogenital sinus. This would explain the perfect formation of the hymen and lower portion of the vagina in our case even though the remainder of the structure failed to develop.

Recapitulation of the evidence suggests, but does not prove, that a genetic fault had been responsible for a confused differentiation of the genital system and that this differentiation, but not growth, had ceased at about the eighth week of gestation. All but two of the anatomic discrepancies or anomalies in this case have been accounted for. The two remaining to be explained are the absence of axillary and pubic hair and the presence of large well-developed breasts.

The significance of the increased development of interstitial cells in cryptorchid testes and in the testes of pseudohermaphrodites has not been satisfactorily explained. If the Leydig cells are the source of the androgenic hormone, as is claimed, one would expect increased masculinization under these circumstances. Such definitely was not the case in this patient. The observations of Cole et al. (18) are of interest in this respect. They reported that in the fetal horse, the testes, which are composed predominantly of masses of interstitial cells, showed a very high concentration of estrogens. Are these cells then the source of the estrogens responsible for the breast development and the cornified vaginal smears? The relatively small amount of estrogen therapy one and one-half years prior to surgery played very little part, as the breasts had been well developed before treatment was instituted. Were the adrenals responsible? Perhaps, but the evidence again indicates that the testes, immature as they were in respect to spermatogenesis, were capable of hormonal activity. Following castration not only did the urinary gonadotropin titer rise and flushes and sweats appear but the breasts definitely became smaller and flabbier; and the vaginal smear, previously normal, showed atrophic cells. The question next arises as to the reason for the moderately increased urinary F.S.H. value in this patient prior to castration. For this we have no explanation to offer unless it be the absence or paucity of Sertoli cells (19). The lack of sexual hair remains to be explained. None has developed under estrogenic ther-

apy. Androgenic therapy has not been tried nor has a skin biopsy been done to ascertain the presence of hair follicles.

Was the castration in this case justifiable? Under the working diagnosis at the time of surgery there was no alternative. In the light of our later conviction it is still justifiable because 1) there was removed prophylactically a statistically important focus for the development of new growths. The occurrence of neoplasms in cryptorchid testes and the gonads of known pseudohermaphroditic individuals is at least twenty times more common than in the population at large (4, 7); and 2) the presence of these abnormal immature gonads contributed nothing which substitution therapy would not adequately provide.

Finally we are faced with the philosophical question: into what category of sex shall we place this individual? Psyche and external habitus were predominately female. Histologically the gonads were male—all male. Yet these testes, from the standpoint of spermatogenesis, had never advanced beyond the fetal stage and hormonally would seem to have exerted more estrogenic than androgenic effects. Upon what, then, does the ultimate basis for the determination of sex depend?

SUMMARY

A case is presented of a 19-year-old girl, tall, with eunuchoid proportions, poorly developed external genitalia, rudimentary vagina, absent clitoris, absent uterus and cervix, absent axillary and pubic hair, moderately high urinary gonadotropin titer and large breasts. Surgical exploration revealed two rudimentary gonads with "attached tubes" and two unfused uterine anlagen. Biopsy of the gonads showed the typical picture of Pick's "adenoma tubulare testiculare." The gonads with their attached tubes and one uterine bulb were removed. Microscopically, the gonads proved to be fetal testes with adenomata, immature seminiferous tubules and a hyperplasia of interstitial cells.

An attempt is made to place the exact time in embryonic life at which all the anatomic deviations occurred. This would appear to be during the eighth week of gestation and to be most likely on a genetic basis.

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THE RELATION BETWEEN INFANT BIRTHWEIGHT AND SUBSEQUENT DEVELOPMENT OF MATERNAL DIABETES MELLITUS

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THAT diabetic women frequently give birth to unusually large infants is well known. Only recently, however, has it been emphasized that infants of excessive weight may be born to mothers *before* clinically apparent maternal diabetes mellitus develops (1). Thus, the average weight of infants born to prediabetic mothers considerably exceeds the normal (2). The combined fetal and neonatal mortality rate is high in the prediabetic group as well as in the diabetic (3), and similar fetal, visceral changes are present in both groups (4). This study was undertaken to ascertain how the birthweight of an unusually large baby can be correlated with the likelihood of the subsequent development of maternal diabetes, and to determine the average time elapsing between the birth of a large baby and the development of clinical diabetes.

METHODS

One hundred parous, diabetic women with an average age of 55.3 years, who remembered the birthweights of their children, constitute the diabetic group (Group 1). These individuals were outpatients of the Washington University Diabetic Clinic or were hospitalized on the medical service of the Barnes Hospital. An equal number of parous women without glycosuria or symptoms of diabetes, from the medical and surgical public wards, served as controls (Group 2). The controls were also largely beyond the childbearing age; their average age was 51.2 years. Each group was asked for the following information:

1. Present age of patient.
2. Age when diabetes developed (diabetics only).
3. Number of pregnancies.
4. Birthweights of each child.
5. Family history of diabetes (patient's and husband's family).
6. Birthweights of the patient and near relatives.
7. Age of the patient at the time of delivery of her first "big baby."

Miscarriages, deaths in utero and premature deliveries were excluded

Received for publication December 13, 1947.

from all tabulations and computations involving Groups 1 and 2. The age at the time of development of diabetes was chosen as that year in which the condition was definitely diagnosed by a physician. Any infant weighing 10 pounds or more at birth was termed "big"; any infant weighing less than 10 pounds was termed "normal" (5). None of the babies in this study was born to a mother clinically diabetic at the time of childbirth. In order to obtain data on a larger group of births, the birthweights of 1000 consecutive babies whose births were recorded as occurring at full term in the St. Louis Maternity Hospital in the year 1927 were used as additional controls (Group 3). The year 1927, although subsequent to the average date of birth of the infants in Groups 1 and 2, was the earliest year for which data were readily available. In compiling the data for Group 3, no attempt was made to exclude from the series births to diabetic women.

RESULTS

Distribution of big infants: Three hundred and sixty children were born to the 100 prediabetic mothers, and 315 were born to the control women of

TABLE 1. BIG INFANTS BORN TO 100 PREDIABETICS AND TO 100 CONTROLS (GROUPS 1 AND 2)

Infant Weight, lbs.	Total Number of Big Infants	Status of Mother					
		Prediabetic		Control, with Positive Family History of Diabetes		Control, with Negative Family History of Diabetes	
		Number of Big Infants	Percentage of Big Infants	Number of Big Infants	Percentage of Big Infants	Number of Big Infants	Percentage of Big Infants
10 or more	144	111	77.1	10	6.9	23	16.0
11 or more	78	68	87.2	4	5.1	6	7.7
12 or more	52	47	90.3	2	3.9	3	5.8
13 or more	24	23	95.8	1	4.2	0	0.0
14 or more	12	12	100.0	0	0.0	0	0.0
15 or more	3	3	100.0	0	0.0	0	0.0

Group 2. A striking correlation between the birth of big babies and the prediabetic state is shown in Table 1. Of the 144 infants weighing 10 pounds or more, 77.1 per cent were born to women destined to develop diabetes. An additional 6.9 per cent were born to Group 2 (control) women with a positive family history of diabetes, whereas only 16.0 per cent were born to Group 2 mothers with a negative family history. Compared to the control series, the preponderance of large infants coming from prediabetic

women increased as the birthweight rose. For example (see Table 1), 87.2 per cent of babies weighing 11 pounds or more were born to prediabetics, and only 7.7 per cent were born to normal women from a nondiabetic family. At the level of a birthweight of 13 pounds or greater, 23 of 24 infants, or 95.8 per cent, came from prediabetic mothers.

Frequency of big infants: Fifty-eight per cent of the diabetic group gave birth to at least one big baby during their prediabetic years. Many prediabetics gave birth to more than one big infant; thus, 111 big babies were born to 58 women. Twenty-seven per cent of the control group gave birth to at least one big baby, but 8 of the 27 were mothers with diabetes in their family. When all those families with diabetes are excluded, it was found that only 24.4 per cent of the remaining group have had at least one large baby. Twenty-six of the 100 diabetic women gave birth to *two* or more big infants. In contrast, only 5 of the Group 2 control women had two or more big infants, but diabetes subsequently developed in the sons of 2 of these 5 women. Thus, only 3 of the control group with a negative family history of diabetes gave birth to two large infants.

Birthweight distribution: The extent to which the prediabetic state influences the birthweight of the infant is also shown in Figure 1. The distribution curve of infant birthweights from the 100 mothers of the control group (Group 2) has its peak between 7 and 8 pounds, and rapidly falls off so that at a weight of 10 pounds only about 2 per cent of the group are included. The distribution curve for the children of the 100 prediabetic mothers (Group 1) is displaced toward the higher weights. Although the peak in this group also occurs between 7 and 8 pounds, the percentage of babies in the higher weight groups is considerably greater than in the controls. Additional data on birthweight are charted in Figure 1, as obtained from a study of 1000 unselected consecutive births occurring in the St. Louis Maternity Hospital in 1927 (Group 3). The birthweight distribution curve of the hospital births corresponds closely to the curve pertaining to the control group of 100 mothers (Group 2).

The average birthweight of children born to our prediabetic mothers was 8.9 pounds or 4.0 kilograms, whereas the average birthweight of the children of the control mothers (Group 2) was 8.0 pounds or 3.5 kilograms. Statistical analysis of the birthweight data shows that the standard error of the difference between the means of Groups 1 and 2 is 0.144 pounds. Calculated on the basis of probability, a difference of 0.9 pounds between means is statistically significant. Our data are, therefore, in agreement with those of Miller (2) in demonstrating that the average birthweight of children born to prediabetic mothers is greater than that of children born to normal mothers.

Latent period: In the 58 of the 100 prediabetic patients who gave birth

to big babies, the average age at the time of birth of the first big baby was 22.9 years. Diabetes was diagnosed at an average age of 47.1 years, and the "latent period" between the birth of the big baby and the development of clinical diabetes averaged 24.2 years. In this series the shortest latent

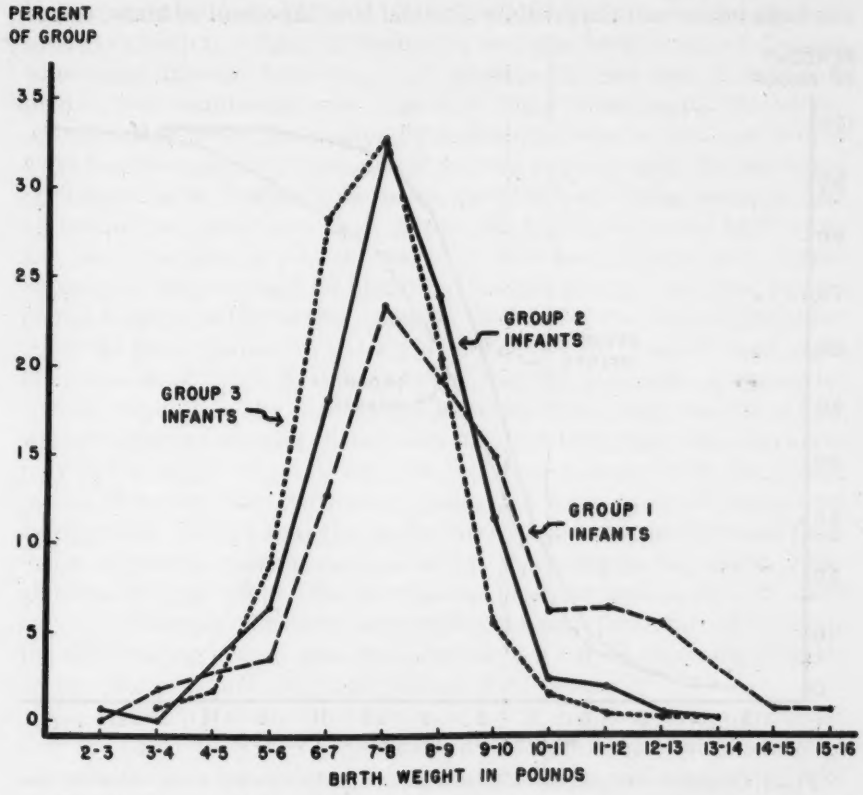

FIG. 1. Birthweight distribution curve of infants born to prediabetic and to control mothers. Dashed line: 360 births to 100 prediabetic mothers (Group 1). Solid line: 315 births to 100 control mothers (Group 2). Dotted line: 1000 consecutive full-term births, St. Louis Maternity Hospital, 1927 (Group 3).

period was 1 year and the longest was 46 years. Only 5 of the 58 patients had a latent period less than 10 years.

Diabetes mellitus developing in big babies: Four of the 144 big babies here reported are known to have developed diabetes at an average age of 18.8 years. In addition, 4 of the 100 prediabetic mothers were themselves known to have been big babies. Thus, there, are 8 cases in which it is def-

initely known that big babies have developed diabetes. Three of these 8 had a negative family history of diabetes but a positive family history of big babies; these 3 developed diabetes at an average age of 27.0 years.

Prediction of maternal diabetes on basis of birthweight of offspring: The data thus far presented clearly demonstrate a relationship between unusually large babies and the prediabetic state. It is important to know, there-

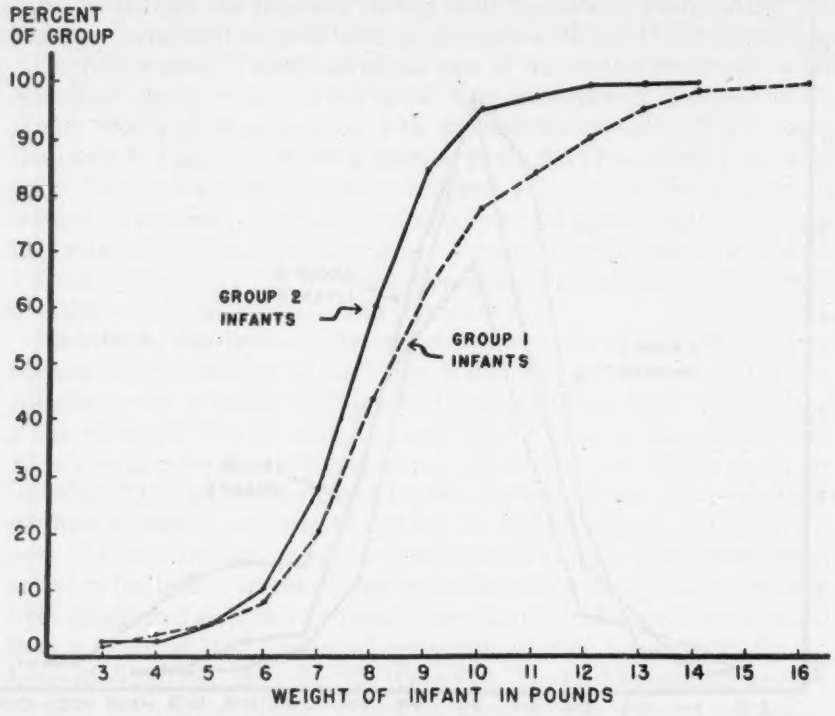

FIG. 2. Cumulative frequencies of infants born to prediabetic and control mothers correlated with birthweight. Dashed line: 360 children of 100 prediabetic mothers (Group 1). Solid line: 315 children of 100 control mothers (Group 2).

fore, whether one is justified in making a prediction of subsequent diabetes in a mother who bears a big baby. If the birthweight data from our diabetic women (Group 1) and our group of controls (Group 2) are used to construct a cumulative frequency distribution curve, or ogive (Fig. 2), the proportion of children above or below any given weight is readily obtained. These curves were constructed by calculating and plotting the percentage of infants weighing 3 pounds or less, the percentage weighing 4 pounds or less, and so on for each weight plotted. For example, from Figure 2 one learns

that 22.0 per cent of the children born to the prediabetic women weighed over 10 pounds, whereas only 4.5 per cent of children born to the controls were of this weight. The average age at which our prediabetic females gave birth to their first large baby was 23 years. A survey of large portions of the population indicates that at this age the chances of a woman eventually becoming diabetic are 42.3 per 1000 (6). If 100,000 women aged 23 years each gave birth to a child, 4230 children would be born to women destined to develop diabetes. According to our findings, 22.0 per cent of these children, or 933, would weigh over 10 pounds. Of the remaining 95,770 children whose mothers would not eventually develop diabetes, only 4.5 per cent, or 4300, would weigh over 10 pounds. If we were to have made the prediction of diabetes in the mother because she gave birth to a baby weighing over 10 pounds, we would have been correct 933 times and wrong 4300 times. Our prediction accuracy would, therefore, have been 17.8 per cent. A similar analysis may be made for higher birthweight groups. Assuming we predicted diabetes in the mother solely on the basis of the birthweight of her child, the prediction accuracy for a given birthweight is as indicated in the final column of Table 2. It is apparent that the prediction accuracy increases steadily as the birthweight increases. Since the chances of any woman aged 23 becoming diabetic are 42.3 per 1000, the prediction accuracy at this age is only 4.23 per cent (6), if one disregards the pregnancy record. However, when the woman's pregnancy record is considered, it can be seen from Table 2 that the prediction accuracy may be increased fourfold to fifteenfold over the usual accuracy, depending on the weight of the abnormally large infant. The calculations made for women aged 23 serve only as an example; the figures are roughly the same for women throughout the childbearing period, since the chances of a female becoming diabetic do not change appreciably until the age of 45 years (6).[1]

The figures in Table 2 should be regarded as only roughly approximate; they are based upon such assumptions as that prediabetic women have as many children as nondiabetic women, that diabetes will not develop subsequently in our control Group 2, and that the chance of developing diabetes is the same for parous women as for nulliparous women. It is uncertain whether our prediction accuracy figures based on women giving birth

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[1] "Prediction accuracy" calculations have also been made on the basis of the incidence of infants observed to be of a specific weight, rather than on the basis of the observed cumulative incidence of infants weighing over a specified weight as described above and presented in Table 2. The "prediction accuracy" figures for mothers bearing a single big infant, correlated with birthweight, when calculated in this manner are as follows: 10 to 11 pounds, 10.7 per cent; 11 to 12 pounds, 13.0 per cent; 12 to 13 pounds. 45.2 per cent; over 13 pounds, 100 per cent.

to babies in about the year 1920 will be equally applicable to mothers giving birth to babies in 1947. It is recognized that birthweight information obtained by interview is not as reliable as that obtained from hospital records. We obtained information from our diabetic women (Group 1) and our controls (Group 2) by identical methods in an attempt to control

TABLE 2. CALCULATED PROGNOSTIC SIGNIFICANCE OF A LARGE INFANT. PERCENTAGE OF MOTHERS AGED 23 YEARS AND BEARING BIG BABIES WHO MAY BE EXPECTED TO DEVELOP DIABETES MELLITUS SUBSEQUENTLY, CORRELATED WITH SIZE OF INFANT

Infant Birthweight in Excess of	Observed Incidence Births of Specified Weight to		Calculated Incidence of Births of Specified Weight to			"Prediction Accuracy"†
	Prediabetics	Controls	Prediabetic Mothers	Normal Mothers	Total Mothers	
Lbs.	Per Cent	Per Cent	per 100,000 births*	per 100,000 births*	per 100,000 births*	Per Cent
10	22.0	4.5	933	4300	5233	17.8
11	16.9	2.3	715	2200	2915	24.5
12	9.5	0.4	401	383	784	51.2
13	3.9	0.1	165	96	261	63.2

* 100,000 births to mothers aged 23, unselected as to normal or prediabetic maternal state; the term "normal" is employed to describe those mothers who will never develop diabetes mellitus.

† Calculated incidence of prediabetic state in mothers bearing baby of specified weight:

$$\left(\frac{\text{calculated prediabetic births}}{\text{calculated total births}} \times 100\right).$$

this factor. It should be added that the prediction accuracy refers only to the possibility of developing diabetes and does not relate to the prediction of *not* developing diabetes.

DISCUSSION

Both maternal and fetal factors must be considered in attempting to establish why fetal giants occur so commonly in the prediabetic state. It is well known that babies tend to be heavier with longer gestational age. Prolonged gestation has been shown (7) not to be common in the diabetic mother, and there is no reason to suspect it in the prediabetic. Maternal

obesity plays a role in the causation of large infants, according to Eastman (8); others assert that neither maternal obesity (2) nor maternal gain in weight during pregnancy (9) are causally related to fetal gigantism. Hyperglycemia in the mother and fetus has been excluded as a cause in the opinion of Miller (2) because, in a series of his prediabetic mothers bearing large babies, no evidence of diabetes presented itself on the basis of urine and blood sugar determinations at the time of delivery. Eastman (10) has often observed diminished glucose tolerance during the postpartum period in "normal" mothers bearing heavy infants. He does not believe, however, that maternal hyperglycemia is the sole cause of these large babies, or even the most important cause. Evidence discounting hyperglycemia as a factor is the finding that experimental diabetes in animals does not lead to fetal gigantism; Miller (11) has recently shown that the birthweights of rats, rabbits, and dogs are normal despite the presence of maternal diabetes induced by alloxan.

Consideration should be given to excessive production of maternal anterior pituitary growth hormone as a possible cause of fetal overgrowth, since hypertrophy of the anterior pituitary and histologic changes in several of its cell types are known to occur in normal pregnancy (5). On the other hand, there is evidence that the pituitary of the fetus itself may play a role in fetal overgrowth. Miller and his co-workers (4, 12, 13) have demonstrated, in babies born to prediabetics, increased numbers of eosinophil cells in the pituitary gland, splanchnomegaly, hyperplasia of the adrenals and islands of Langerhans, and hyperplasia of the female genital organs, all of which findings suggest anterior pituitary overactivity. Still another explanation for fetal gigantism, which allows for both maternal and fetal factors, has occurred to us. The fetus may have an inherited defect, possibly transmitted by *either* parent, which makes it unusually susceptible to normal stimulation by the maternal pituitary. Thus, although it may be true that maternal endocrine functions are responsible for the anatomic changes in the giant fetus, it does not necessarily follow that these maternal functions are abnormal, or that the assumed defect in the fetus is located in its pituitary.

SUMMARY

1. We have analyzed the birthweight data on infants born to 100 women destined later to develop diabetes mellitus and on infants born to two control groups.

2. Our findings, many of which corroborate the reports of others, lead us to conclude that:

a. The birth of an infant weighing over 10 pounds may herald the development of diabetes in the mother.

b. The average birthweight of infants born to prediabetic mothers is greater than that of infants born to normal mothers.
c. Women developing diabetes after the childbearing period are recruited to a large extent from those mothers who give birth to babies weighing over 10 pounds.
d. Abnormally large babies are born to prediabetic women more frequently than to normal controls.
e. The period between the birth of the first abnormally large infant and the development of clinical diabetes in the mother averaged about 24 years in our series, with a range of from 1 to 46 years.

3. On the basis of our data, a table has been constructed permitting rough estimation of the accuracy with which one may predict the subsequent development of diabetes in a woman giving birth to a baby having a specified weight in excess of 10 pounds. It shows that as the birthweight of the baby rises, the prediction accuracy increases progressively and is greater than 60 per cent when the baby weighs more than 13 pounds.

ACKNOWLEDGMENT

The authors are indebted to Dr. Willard M. Allen of the Department of Obstetrics and Gynecology, to Dr. Florence Heys of the Department of Pediatrics and to Mrs. Samuel Weissman of the School of Social Work of Washington University, and to Dr. N. J. Eastman of the Department of Obstetrics, Johns Hopkins University, for helpful suggestions in planning and reporting this work.

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EXTREME LEYDIG CELL HYPERPLASIA ASSOCIATED WITH TWO OTHER ENDOCRINE CHANGES*

A CASE REPORT

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INTRODUCTION

STUDIES of the Leydig cells of the testes have, to date, resulted in extreme confusion. Although the histology has been well described there are numerous and conflicting reports about their embryology, physiology and pathology. It would, therefore, be well to collect cases of the pathologic states of these testicular interstitial cells and to attempt to correlate them with some of the clinical endocrine changes.

CASE REPORT

The patient, a 54-year-old white farmer, developed hallucinations in 1929 and was first admitted to a neuropsychiatric hospital on June thirteenth of that year. His case was diagnosed as dementia praecox, hebephrenic type. He was single, and nothing unusual was noted about his sex habits. His use of alcohol was moderate, and he used snuff regularly. Venereal disease was denied. As a child he had mumps and pertussis. It is not known if there was orchitis with the mumps. He was said to have had small testes since childhood.

Physical Examination: At the time of admission his temperature was 98° F.; pulse, 90 per min.; blood pressure 100/62; respirations, 20 per min.; height, 70¼ inches, and weight, 163 pounds. He had black hair, blue eyes and a clear skin. He was well developed, and his musculature was good. Eye, ear, nose and throat examination showed only a slight hypertrophy of the left inferior turbinate. The thyroid gland was not enlarged. The heart, lungs and abdomen were normal. The testes were small and firm, no larger than those of a 10-year-old boy. The penis was normal in configuration and size, and the prepuce retracted well. No abnormalities of the extremities were noted. Both internal and external hemorrhoids were present.

Accessory Clinical Data: The complement fixation test for syphilis was

Received for publication January 12, 1948.

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negative. Urinalysis showed no sugar or albumen, in an acid urine of S.G. 1.027. The blood count was within normal limits.

In 1934 the patient was transferred to this hospital, and shortly thereafter a diagnosis was made of pulmonary tuberculosis, chronic, bilateral, moderately active, with cavitation in the left infraclavicular region. At that time results of the physical examination were essentially the same as five years previously, except for the chest findings. An examiner again

FIG. 1. Right adrenal, showing large cortical adenoma ($\times 2\frac{3}{4}$).

noted that the testes were small and undeveloped. The patient had well developed muscles, an average type of masculine voice and a male distribution of hair. It was noted that there were no evidences of endocrine disturbances.

The course of the tuberculous process was progressive. On March 3, 1947, the patient developed a tension pneumothorax and expired rapidly.

Autopsy Findings: (Only the pertinent findings are included.)

Gross Findings: The body was that of a well built, well nourished adult white male. The musculature was well developed. There was a normal male distribution of hair and no evidence of gynecomastia. In the pleural cavities there were dense, fibrous adhesions at both apices. Most of the

left lung was atelectatic and there was a large cavity and numerous smaller cavities in the apex. The entire right lung was atelectatic. There was an acute bronchitis, and mucopurulent material occluded the smaller bronchi in both lungs. The left adrenal gland was normal grossly. The right adrenal contained a well circumscribed cortical adenoma, 1.7 cm. in diameter (Fig. 1). It was bright, golden yellow and showed no areas of hemorrhage or necrosis. The adenoma was well demarcated from the adjacent cortex. The penis was well developed. The scrotum contained two small testes approximately equal in size. Only the right testis was removed and this measured

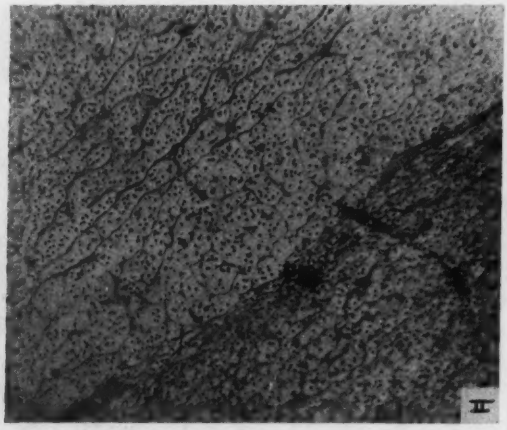

FIG. 2. Junction of adenoma with adrenal cortex. Hematoxylin and eosin (×60).

15×12×10 mm. It was firm and cut with moderate resistance. The tubules could not be strung out. The prostate was small and firm. The brain and the pituitary gland grossly showed no lesions.

Microscopic Findings: Sections of the lungs showed large areas of caseous necrosis with tubercle formation. There was much scarring, atelectasis, and some small patchy areas of emphysema. The larger bronchi contained purulent material in the lumina, and many mononuclear cells in the walls obscured the structure. There was destruction of the mucosa of a bronchus lying adjacent to an area of caseous tuberculosis.

Section of the left adrenal showed only some delipoidization of the cortex. The right adrenal contained a large oval mass separated from the rest of the cortex by thin strands of fibrous tissue (Fig. 2). The mass was composed of cords of large polyhedral cells with a clear cytoplasm and small dark nuclei. The mass was very vascular and was a well organized tissue.

The cortical cells of this adenoma and the remainder of the adrenal cortex showed delipoidization.

Section of the right testis showed no evidence of spermatogenesis. Nu-

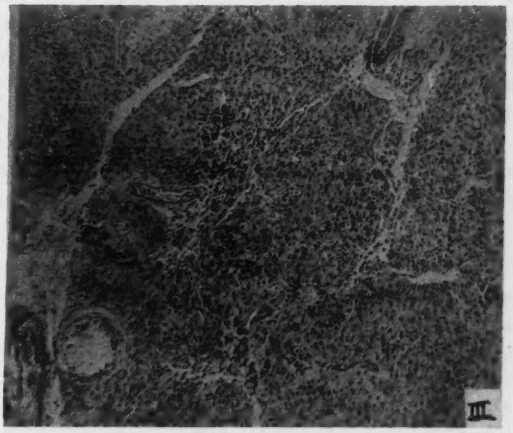

FIG. 3. Section of right testis showing marked interstitial cell hyperplasia and absence of tubules. Hematoxylin and eosin (×60).

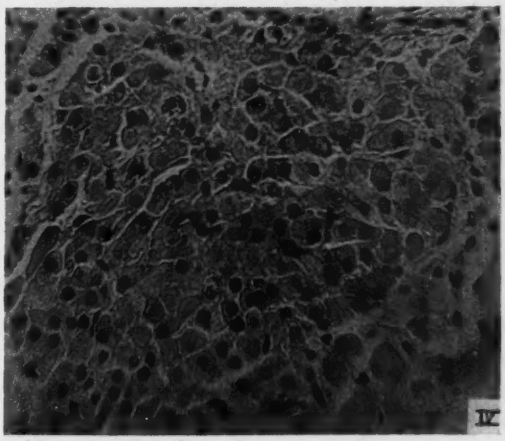

FIG. 4. Interstitial cells of the right testis. Hematoxylin and eosin (×244).

merous sections showed only occasional tubules (Fig. 3). The basement membranes of some of these tubules were hyalinized and thickened. The epithelium lining the tubules was tall and irregular in shape with clear cytoplasm and small pyknotic nuclei. The entire bulk of the testis was composed

of numerous cell masses separated by small amounts of loose fibrous tissue (Fig. 4). There was no definite relationship of these cell masses to the blood vessels. The cells comprising these clumps were large, round and irregularly polyhedral. The nuclei were large, spherical, wrinkled and contained coarse chromatin granules and one or two large nucleoli. Some cells were binucleated. The cytoplasm of these cells was eosinophilic and in many instances contained a large amount of granular brown pigment. Crystalloids and refractile lipoid granules were not seen. The tunica albuginea and epididymis showed no interstitial cells and no changes. Sections of the prostate gland showed no changes.

TABLE 1. DIFFERENTIAL CELL COUNT OF PITUITARY GLAND

Cells	Cell Count		Per Cent of Total
A. Total cell count			
Normal alpha cells	320		
Pyknotic alpha cells	136		
Total alpha cells		456	34.7
Normal beta cells	124		
Pyknotic beta cells	47		
Degranulated beta cells	37		
Total beta cells		208	15.8
Total chromophobe cells		651	49.5
Total cells—all types		1315	100.0
B. Normal cell count			
Normal alpha cells	320		29.2
Normal beta cells	124		11.3
Normal chromophobe cells	651		59.5
Total normal cells		1095	100.0

A differential cell count was done on the pituitary gland.[1] The findings are given in Table 1 and they are analyzed in two ways: (A) the "total cell count," which may show the preterminal distribution; and (B) the "normal cell count" (undegenerated cells) which may show the terminal condition. It is not possible to say how long the preterminal condition existed. If one assumes that the pyknosis is not a postmortem change (the patient was embalmed immediately after death and the autopsy was performed

[1] By Dr. H. N. Marvin, Department of Anatomy, University of Arkansas.

seven hours later), then the normal cells plus pyknotic cells in each group gives the preterminal distribution. This showed a mild basophilic hyperplasia which is considered compatible with deficient production of male sex hormones. On the other hand, 24 per cent of the beta cells and 28 per cent of the alpha cells are pyknotic. This shows that the alpha and beta cells were undergoing degeneration at the same rate at the time of the autopsy. This could reasonably be interpreted as a degeneration resulting from terminal collapse. The results of the pituitary differential cell count are suggestive of hypogonadism.

Anatomic Diagnosis: Bilateral caseous tuberculosis with cavitation on the left; fibrous pleural adhesions; old and recent needle punctures in the thoracic wall, bilaterally; bilateral pneumothorax and bilateral compression atelectasis. Acute and chronic bronchitis with ulceration and mucopurulent material occluding the bronchi. Acute congestion and edema of the liver with beginning necrosis. Acute congestion of the spleen, fibrous peritoneal adhesions, Cortical adenoma of right adrenal. Atrophy of the testes with hyperplasia of the interstitial cells. Mild basophilic hyperplasia of the pituitary gland. Small scar in medulla and retention cysts of the left kidney.

DISCUSSION

The case presented shows more than a simple hyperplasia of the interstitial cells. The hyperplasia here is so great that the question of neoplasia may be legitimately raised. There is destruction and replacement of the tubules by the interstitial cells. This patient does, however, show those clinical findings ordinarily associated with hyperplasia, namely, small testes, age past 45 years, and the presence of a chronic debilitating disease.

There are associated endocrine factors in this case. There is an increase in the basophilic cells of the pituitary. The cortical adenoma of the adrenal is well formed and morphologically appears capable of being a functional tissue. The exact role of the adrenal in relation to the testis and pituitary is purely speculative.

An interesting feature of hyperplasia of the interstitial cells of the testis is the lack of associated virilism. Most patients with this change appear to be either normal or slightly eunuchoid (1) (2). The small testes are due to atrophy of the seminiferous tubules which comprise the greatest mass of testicular tissue.

The effect of interstitial cell tumors is not consistent. A case of gynecomastia associated with an interstitial cell tumor is reported by Hunt and Budd (3). On the other hand, three cases of precocious puberty occurring in cases of interstitial cell tumors are reported by Stewart, Bell and Roehlke (4). This conflict emphasizes the lack of full understanding of the nature and functions of the Leydig cells.

The normal or eunuchoid appearance is not what would be expected in a patient with testes showing hyperplasia of cells supposedly capable of producing an androgenic substance (testosterone), which is credited with the development of the male secondary sex characteristics. Thus it appears that the hyperplastic cells are nonfunctional. The possibility of a secretion from the seminiferous tubules must be considered.

An interesting corollary to the findings in this case is reported by Rasmussen (5). Seven patients with basophilism (not pituitary adenomas) were examined with special reference to the adrenals. Three showed change suggestive of cortical adenomas, two had cortical adenomas and two had pronounced hypertrophy of histologically normal cortices.

Our patient shows both the basophilism and the adrenal cortical adenoma. The relationship of these changes to the interstitial cell hyperplasia is, at present, speculative (6).

SUMMARY

A case of unusual hyperplasia of the interstitial cells of the testis is presented.

Other interesting endocrinologic features of the case are presented, namely, a basophilic hyperplasia of the pituitary gland and an adenoma of the cortex of one adrenal gland.

Some of the questions posed by the various endocrine changes are discussed.

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NECROPSY STUDY OF A CASE OF TURNER'S SYNDROME

A CASE REPORT

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TURNER (1) in 1938 described a syndrome characterized by 1) arrest or great delay in growth and ossification (dwarfism), 2) great delay in sexual development (infantilism), and 3) congenital webbing of the neck and cubitus valgus.

CASE REPORT

In 1945 one of us (2) reported a case of this syndrome. The patient was a white female, 20 years old, with primary amenorrhea. Her father was an alcoholic. She was born prematurely. Her feeding was artificial and insufficient, and her somatic development had been retarded since birth. When she was 6 years old she suffered a cranial trauma with loss of consciousness. Two years later she had diphtheria. The serum with which she was treated caused serum sickness.

Physical Examination: The body measurements were those of a girl 8 years old. Her face had a peculiar aged appearance, and the somatic proportions were definitely eunuchoid. She had a congenital webbed neck, and neither mammary development nor sexual hair. The external genitalia resembled those of a girl 3 to 5 years old. The uterus was about the size of a hazelnut. In the upper extremities a pronounced cubitus valgus was noticed.

Roentgenograms of the skull, hands and ankles revealed a bone age between 10 and 14 years.

A vaginal smear showed pronounced estrogenic deficiency with complete absence of cornified cells. Urinary excretion of 17-ketosteroids in 24-hour urine specimens was, on the average, 3.5 mg. The basal metabolic rate was within normal limits.

We could not perform quantitative gonadotropic hormone assays, but we injected the patient's urine into a female rabbit, previously isolated for a month, according to the usual technique. This caused the appearance of a great number of primary follicles in the animal's ovaries. Thus an increased urinary excretion of gonadotropic hormone was demonstrated.

Following the therapy recommended by Albright et al. (3) and Hamblen (4), we treated the patient with stilbestrol and small doses of desiccated

Received for publication November 25, 1947.

thyroid. She grew 1.5 cm., and her body weight increased 1.5 Kg. after three months of treatment.

An intercurrent attack of acute appendicitis warranted a laparotomy. The appendix and a small piece of the left ovary were removed. The patient died twenty hours after the operation in what appeared to be acute cardiovascular shock.

Autopsy Findings: The autopsy was done three and one-half hours after death. The body had an infantile appearance with scanty mammary and genital development. A surgical median scar was noted on the abdominal

FIG. 1. Brain.

wall. The appendix and a small piece of the left ovary had been removed (biopsy).

The positive autopsy findings were as follows:

1. The shortness of the neck was due to a congenital luxation of the atlanto-odontoid joint. The brain surface was normal grossly (Fig. 1).

2. The internal genitalia were infantile. The uterus measured 3.5 cm. (⅔ cervix, ⅓ fundus). The ovaries were fusiform bodies weighing barely 2.5 Gm. each.

3. Lymphoid tissue was abundant in the inguinal and axillary regions, mesentery, Waldeyer's ring and Peyer's patches.

4. There was marked lymphoid hyperplasia in the mucosa and submucosa of the appendix. This was evidently related to the acute symptoms of appendicitis (Fig. 2).

5. In all the organs there were signs of acute vascular shock.

Macroscopic and Microscopic Findings in Endocrine Glands: These findings are of particular interest since there appears to be no other detailed report of an identical case. The cases reported by Rössle and Wallart (5), Hegar (6), and Hegar and Freund (7), do not correspond exactly with this clinical entity.

The pituitary was normal grossly. We observed no regression, or alterations of the stroma or vascular system of the gland. The anterior lobe ap-

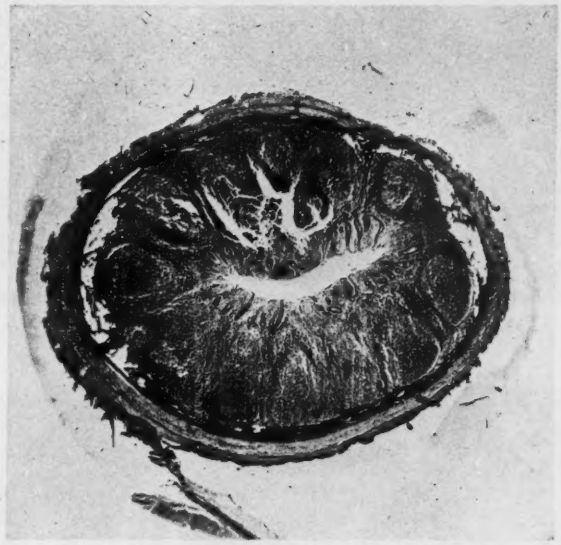

FIG. 2. Vermiform appendix. Hem-eos. ×12.

peared to consist of cellular cordons arranged in follicles. They formed small cavities containing acidophil colloid (Fig. 3). Acidophil and chromophobe cells were predominant, whereas the basophil cells were scanty (Fig. 4). There seemed to be an abnormally high proportion of acidophil cells, but no cell count was made to validate this impression. Proportions of the different cell types in the anterior lobe vary greatly, according to the different techniques used by different observers; hence we did not think it wise to draw any conclusions as to the functional status of the gland (8–13).

The thyroid was small. The follicles measured from 100 to 200 microns in diameter, the epithelial cells being low and the colloid abundant. There were several lymphoid follicles present (Fig. 5).

The pancreas was normal grossly. The islands of Langerhans were normal

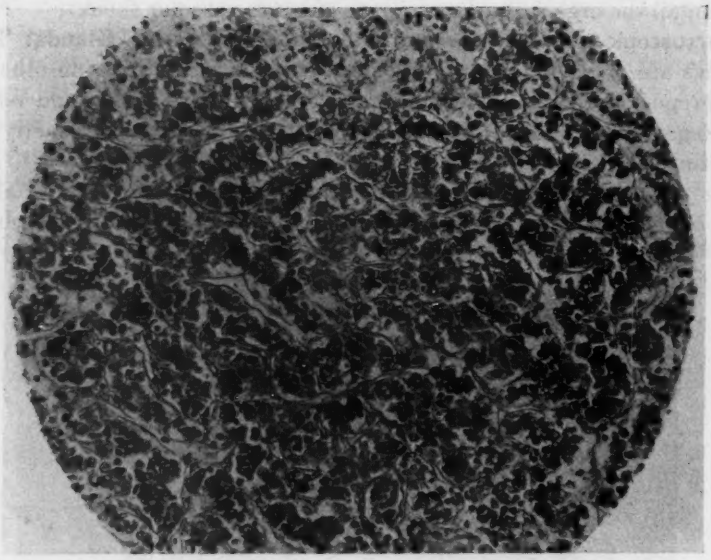

FIG. 3. Anterior lobe of the pituitary. Hem.-eos. ×200.

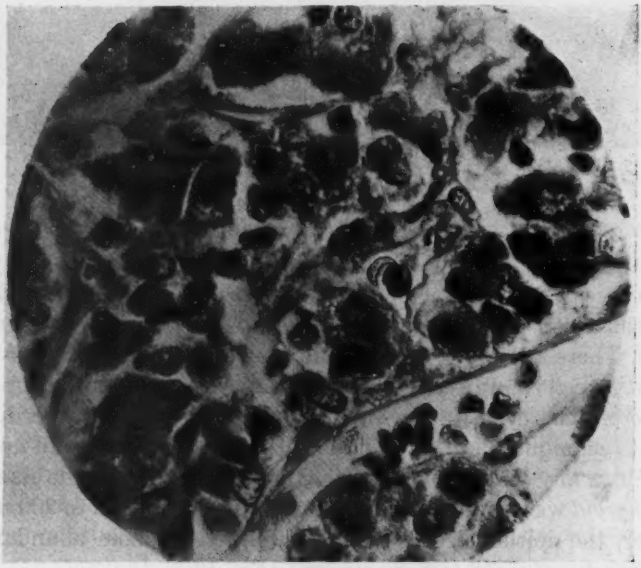

FIG. 4. Anterior lobe of the pituitary. Hem.-eos. ×800.

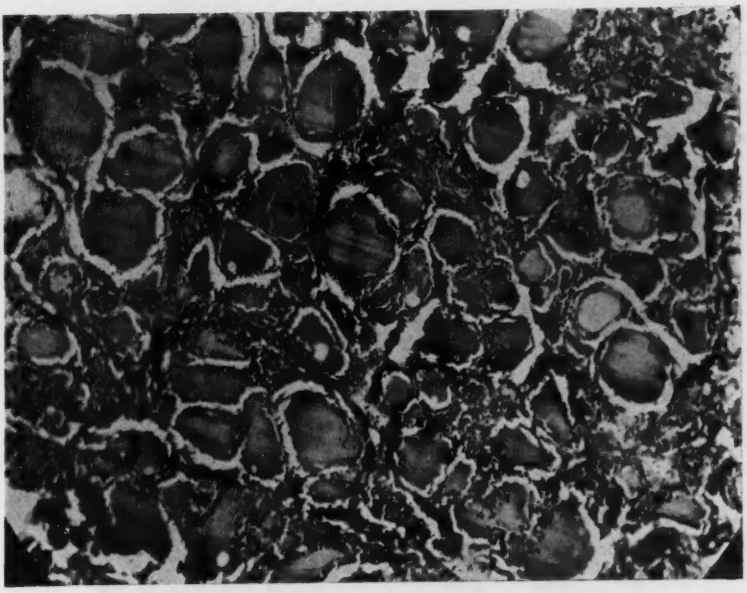

FIG. 5. Thyroid. Hem.-eos. ×80.

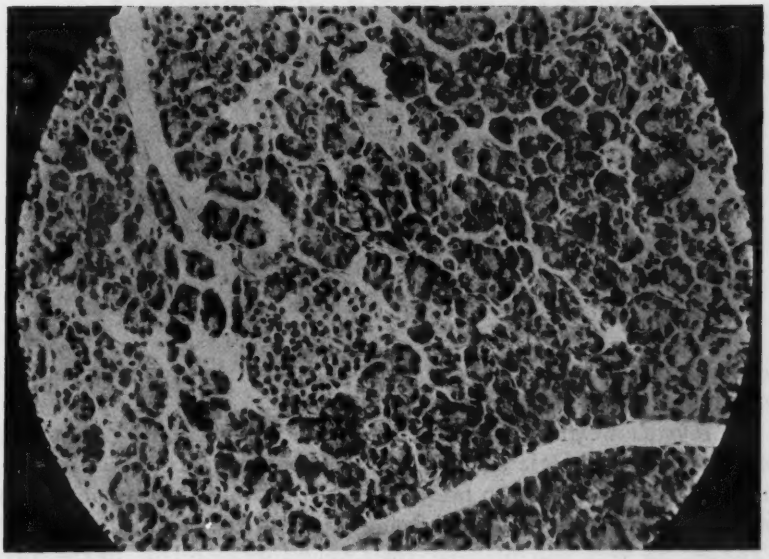

FIG. 6. Pancreas. Hem.-eos. ×200.

microscopically, and alpha and beta cells could be easily distinguished (Fig. 6).

The suprarenals weighed 2.5 Gm. The ideal weight should be 11 Gm. according to the chronologic age of the patient and 7 Gm. according to the somatic age (14). Microscopically the general structure was intact, the

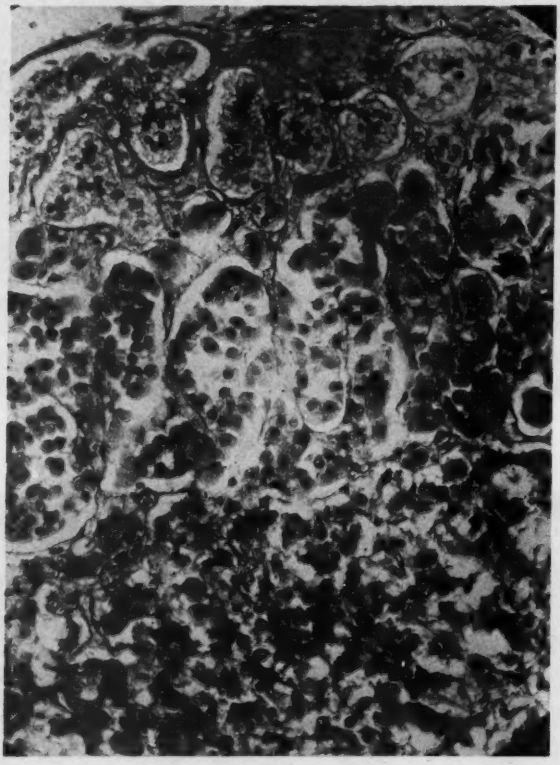

FIG. 7. Suprarenal cortex. Hem.-eos. ×200.

medullary part being well developed (Fig. 7). The cortical section appeared hypoplastic, especially in the glomerular zone.

The thymus weighed 35 Gm. which was excessive for the patient's chronologic and somatic age. The histologic appearance was typically infantile with no tendency to fatty degeneration, and the parenchyma was well developed, the cortical zone being predominant (Fig. 8).

The ovaries were also infantile; their weight was 2.5 Gm. In the cortical part many primary follicles were seen; in the central part well developed

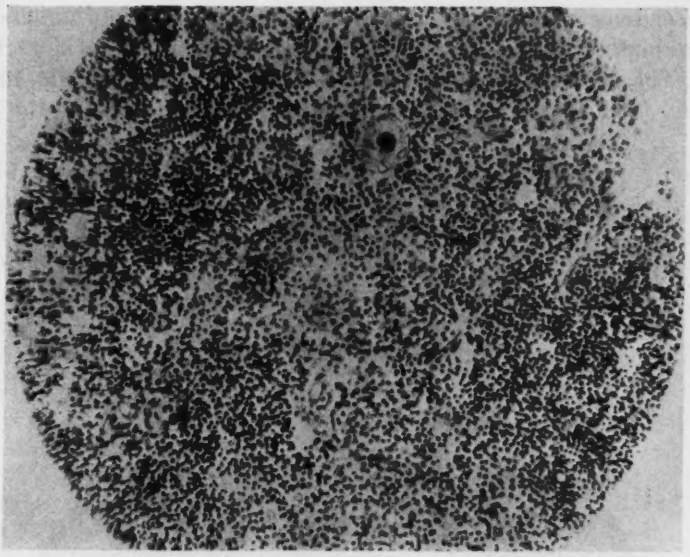

FIG. 8. Thymus. Hem.-eos. ×30.

FIG. 9. Ovary. Hem.-eos. ×15.

follicles with a tendency to cystic degeneration were present. No rupture or luteal changes were noted. The absolute lack of growing and intermediate follicles was striking (Figs. 9, 10).

The endometrium of the uterus was also infantile in character, 150 microns high, with ramified glands of high epithelium and acidophil cytoplasm. The stroma was latent in development, with very few cells (Fig. 11).

FIG. 10. Ovary. Hem.-eos. ×5.

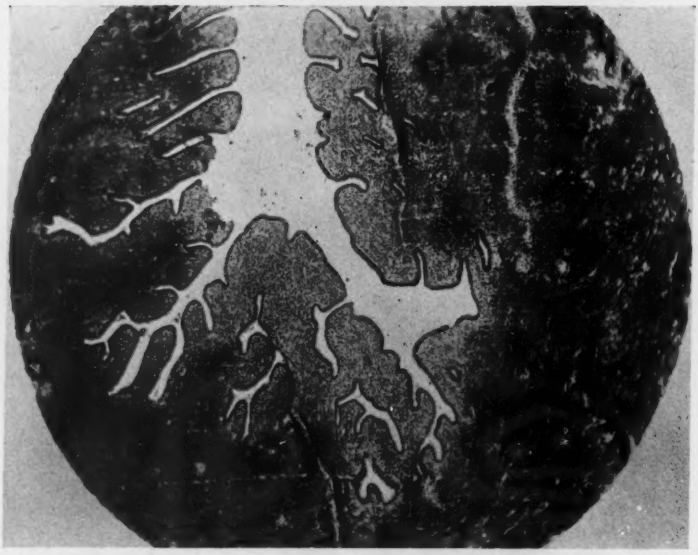

FIG. 11. Uterine endometrium. Hem.-eos. ×45.

DISCUSSION

These anatomic findings supported our diagnosis. To explain the pathogenesis of the symptoms and signs on the basis of an intrinsic ovarian failure alone does not seem logical to us. Hamblen (4) also rejects this explanation. We suggest that the cause originates outside the ovary and is a congenital developmental defect affecting principally the ovaries and suprarenals. On this basis the retarded development of the patient continued, ending in a dwarfism with eunuchoid proportions.

The large thymus and general lymphoid hyperplasia may be related to the hypoplasia of the adrenal cortex. This hypoplasia may bear some relation to the inability of the patient to react adequately to the stress of the appendectomy.

SUMMARY

a. The necropsy and microscopic findings in a case of Turner's syndrome are reported.

b. The anterior pituitary gland was normal grossly. A congenital luxation of the atlanto-odontoid joint, and ovarian and suprarenal hypoplasia were noted. These findings seem adequate to explain the peculiar characteristics of the dwarfism and infantilism.

c. It is suggested that a congenital unknown cause interfered with normal embryologic morphogenesis, affecting principally the gonads and suprarenals, and in a lesser degree the rest of the endocrine system.

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INDUCTION OF UTERINE BLEEDING IN AMENORRHEA WITH A SINGLE INJECTION OF PRECIPITATES OF ESTRONE AND PROGESTERONE

BERNHARD ZONDEK AND SAMUEL ROZIN

From the Department of Gynecology and Obstetrics, Rothschild Hadassah University Hospital, and the Hormone Research Laboratory, Hebrew University, Jerusalem, Palestine

HITHERTO it has generally been thought that to induce bleeding, the uterine mucosa had first to be stimulated to proliferation by estrogenic hormone and that the secretory phase had subsequently to be induced by progesterone. The doses required for this effect were from 30 to 40 mg. of estradiol benzoate and from 25 to 40 mg. of progesterone. This course of treatment lasted for twenty-four days, and required eight injections of 5 mg. each of estradiol benzoate over a period of twenty days followed by daily injections of 5 mg. of progesterone for five days. In many cases bleeding set in a few days after the injections had been discontinued. With this form of therapy the patient received thirteen injections in one month. We think that such a course should be avoided for the following reasons: 1) The prolonged treatment, which makes the patient dependent on the physician for a long period, intensifies the inferiority complex from which the amenorrheic woman already suffers. 2) The 40 mg. of estradiol benzoate necessary for the proliferation of the uterine mucosa exerts an inhibiting effect on the gonadotropic function of the anterior lobe of the pituitary (1), a result which is unconditionally to be avoided in amenorrheic women. If such treatment be continued for several months, the large doses of estrogens cause more harm than benefit, since, although uterine bleeding is thereby induced by local action on the uterine mucosa, at the same time spontaneous regeneration of the gonadotropic function of the pituitary gland is prevented.

In 1942, Zondek (2) recommended a simplified treatment of amenorrhea. The formerly held view that bleeding can be induced only with the aid of progesterone acting on a uterine mucosa previously brought to full proliferation by estrogens, was shown to be incorrect. In normally menstruating women it was found that the administration of 50 mg. of progesterone on the fifth to the tenth day of the cycle brought on a bleeding in the intermenstruum lasting from four to five days ("intracyclic bleeding"), which was considered by the patients to be similar to a normal menstruation

Received for publication October 7, 1947.

(3, 4). Anatomic examination demonstrated that such bleedings had their origin in a typical, thin, intermenstrual mucosa, containing few glands and no glycogen. It was thereby shown that progesterone alone is capable of inducing a bleeding even in an undeveloped mucosa and that the proliferation induced by estrogens is not an essential prerequisite in the bleeding mechanism.

These observations were then utilized in the treatment of amenorrhea. It was surprising to find that it required only two to five days of treatment, with a total dose of 50 mg. of progesterone, to induce bleeding in amenorrheic women. The dose of progesterone could be reduced to 25 mg., if 2.5 mg. of estradiol benzoate were administered concurrently, in cases of amenorrhea which were of not more than two years' duration. It should again be emphasized that in this simplified method, bleeding originates in a thin mucosa, only slightly proliferated. A minimal estrogen stimulus seems, however, to be necessary in primary amenorrhea since progesterone

TABLE 1. SIMPLIFIED TREATMENT OF AMENORRHEA WITH HORMONE SOLUTIONS

Days of Treatment	Estradiol Benzoate, mg.	Progesterone, mg.
Primary Amenorrhea		
5	2.5–5	50
Secondary Amenorrhea		
Of more than 2 years' duration		
5	—	50
2	—	50
Of less than 2 years' duration		
2	2.5	25

alone is incapable of inducing bleeding, and from 2.5 to 5 mg. of estrogens must be administered together with the 50 mg. of progesterone in the 5-day treatment of such cases. Results with our simplified method are summarized in Table 1. Our experience with this method of treatment of amenorrhea has been corroborated by Berlind (5), Finkler (6), Rakoff (7), and others.

METHOD FOR SINGLE-INJECTION TREATMENT

The following data demonstrate that the treatment of amenorrhea may be further simplified and that a single injection may be substituted for the two to five injections hitherto required to induce bleeding. This can be achieved if estrone and progesterone be injected not as a solution but as

very minute crystals (estrone) or in amorphous form (progesterone). The mechanism of action will be reported in another paper, and only brief mention will be made of this matter in this article. Estrone and progesterone are dissolved in an organic solvent miscible with water (a mixture of various homologous ester derivatives of α-β-dichlorhydrin), and the hormones are precipitated from this solution in the syringe by the addition of saline solution.[1] The crystals are precipitated in so fine a form that they do not occlude the lumens of the needles used for intragluteal injections. Constancy of size of the precipitated crystals is insured by an optimum proportion between the solution of the hormones and the precipitator. The fact that the size and form of the hormone crystals have undergone a change as a result of precipitation is shown by the following observations: a) crystallized estrone, which generally occurs in rhombic form, is precipitated by this process in the form of delicate, ice-fern-like needles; b) progesterone, generally in the form of prisms and needles, is precipitated in amorphous form, and crystals begin to form again only after a considerable length of time; c) the mixture of estrone and progesterone is also precipitated in amorphous form, and from this suspension progesterone crystals in particular are redeposited after the lapse of a certain period. Twenty-four hours after the precipitates are injected subcutaneously into rats few crystals of estrone can be found, whereas many more crystals of progesterone, recrystallized from the injected mixture, are observed. If crystals of estrone and progesterone in their original form are suspended in water, in which form the crystals are considerably larger than in our preparations, bleeding cannot be induced in amenorrheic women by a single injection. It follows that the size of the crystals is of decisive significance.

RESULTS

We have excluded from our series those cases in which amenorrhea was but a symptom of general disease, for example, tuberculosis, diabetes and avitaminosis. In the patients treated, amenorrhea had either lasted an average of four years (secondary amenorrhea) or the women had never menstruated (primary amenorrhea). In all cases there was a distinct disturbance in the development of the genital organs, atrophy of the vagina and especially a definite hypoplasia of the uterus, which was reduced to as little as 3 cm. in length. The fact that production of estrogenic hormone was diminished or nonexistent was proved by increased excretion of follicle-

[1] We are indebted to "Teva," Middle East Pharmaceutical & Chemical Works, Ltd., Jerusalem, for supplying us with the preparation (Ambo-Pell ...ds).

stimulating hormone in the urine (8) in all the patients with primary amenorrhea and in some of the patients with secondary amenorrhea (100 M.U. or more per liter of urine). There was no development of the uterine mucosa, as investigated by the progesterone test (3), in all patients with primary and in some with secondary amenorrhea; that is, 50 mg. of progesterone did not induce bleeding, which resulted only after the administration of additional estrogenic hormone. In all our patients, strip curettage showed the uterine mucosa to be underdeveloped, the mucosa being thin and containing a few glands only in the postmenstrual phase. The vaginal smear showed diminished or absent estrogenic activity. There were a few patients with secondary amenorrhea showing signs of mild hypothyroidism combined with adiposity, who responded promptly with bleeding during our treatment.

A detailed report will be published elsewhere.

Primary amenorrhea

We treated 5 patients with primary amenorrhea.

Patients 1 and 2 each received 5 mg. of estrone and 50 mg. of progesterone in a single injection, and both reacted after nine and ten day intervals, respectively, with bleeding lasting for four days.

Patient 3 did not react. This patient was a 37-year-old woman, who had already received several courses of hormone treatment of as much as twenty days' duration without success.

Patient 4 received three treatments at monthly intervals, each treatment consisting of 5 mg. of estrone and 50 mg. of progesterone. The patient responded every month with bleeding ten days after each injection. Although she received no treatment the fourth month, a spontaneous bleeding occurred after an interval of twenty-four days. Since this time the patient has menstruated spontaneously four times, at intervals of twenty-five to twenty-eight days. The fact that *spontaneous* bleeding was observed in a case of primary amenorrhea suggests that our treatment may not only constitute substitution therapy but may actually serve as a stimulus of the gonadotropic function of the anterior pituitary lobe, which regulates the bleeding mechanism. Similar results were obtained in the treatment of secondary amenorrhea, as reported in the next section.

Patient 5 was initially treated with 8 injections of 40,000 U of estradiol benzoate together with 5 mg. of progesterone over a period of twenty-four days, but bleeding could not be induced thereby. This patient was a 20-year-old girl in whom secondary sex characteristics were totally absent. After rectal examination, it was still doubtful whether or not a uterus was present, but the introduction of a speculum revealed a cervix the size of a pea. This observation justified the assumption that a minute uterus did

exist. This patient received 10 mg. of estrone together with 50 mg. of progesterone in a single injection. Ten days later bleeding began, and continued for a six-day period. After a second treatment with 5 mg. of estrone together with 50 mg. of progesterone, bleeding occurred after an interval of seven days.

Secondary amenorrhea

We have found in cases of secondary amenorrhea that, in order to induce bleeding, larger doses of progesterone must be given in the first treatment but that these doses may be reduced in the second and third treatments. This observation seems to be of interest, inasmuch as it shows that the body may have been rendered more sensitive to the action of the hormone.

A patient with secondary amenorrhea responds with bleeding after the injection of 5 mg. of estrone and 50 mg. of progesterone or, in milder cases, of 50 mg. of progesterone alone. The progesterone dose may then be reduced by half in the second and third treatments, when 5 mg. of estrone and 25 mg. of progesterone suffice. According to our experience to date, we recommend from three to four treatments at monthly intervals in order to imitate the normal cycle. After such a course 5 of our 29 patients treated for secondary amenorrhea have to date menstruated spontaneously. One of them menstruated three times, and 4 of them twice each, after intervals of twenty-two and twenty-seven days, respectively. Spontaneous bleeding in a case of primary amenorrhea has been reported in the previous section. The fact that cyclic estrone-progesterone treatment is capable of inducing spontaneous bleeding in subsequent months supports the view that such treatment may stimulate the gonadotropic function of the anterior pituitary lobe, so that the machinery of sexual function is again set in motion. It is noteworthy that G. V. Smith (9) recommends cyclic treatment as the method of choice to re-establish a normal interrelationship between the pituitary gland and the ovaries.

Our single-injection method of treatment is satisfactory even in severe cases of secondary amenorrhea, as may be seen from the fact that 3 patients, having amenorrhea for nine years, regularly responded with bleedings lasting from three to five days during twelve treatments. Bleeding was induced five times in a woman who had amenorrhea for five years; and 3 patients who had amenorrhea for four years were successfully treated. In addition, among 10 women who had amenorrhea for three years, 8 responded with bleedings. Since the average duration of amenorrhea in our cases was four years, it is clear that we did not select mild cases. Only 3 patients who had amenorrhea lasting for less than two years received this treatment.

SUMMARY

To date 34 patients with amenorrhea have been treated.

a) Five patients with primary amenorrhea received eight treatments, of which seven (87.5 per cent) were successful.

b) Twenty-nine patients with secondary amenorrhea received forty-three treatments, of which forty (93 per cent) were successful. Bleeding began from seven to ten days after injection and lasted for an average of four days.

CONCLUSIONS

1) A new treatment of amenorrhea with a single injection of estrone and progesterone has been described. Estrone and progesterone, dissolved in an organic solvent, are precipitated in the syringe by the addition of saline solution, the suspension being injected intragluteally.

2) The doses of hormone required in the single-injection treatment of primary amenorrhea are 5 to 10 mg. of estrone and 50 mg. of progesterone.

3) The doses of hormone required in the single-injection treatment of secondary amenorrhea are as follows: In the first treatment 5 mg. of estrone and 50 mg. of progesterone should be administered. In the subsequent treatments the dose of estrone remains the same, but the dose of progesterone may be reduced to 25 mg.; or 50 mg. of progesterone without estrone may be used. This decreased requirement may indicate that the body has been rendered more sensitive to the hormones.

4) Three to four treatments at intervals of four weeks should be given, and spontaneous bleeding should then be awaited. We observed spontaneous cyclic bleeding in 5 patients with secondary amenorrhea and in 1 patient with primary amenorrhea. This leads us to assume that the treatment not only constitutes a substitution therapy, but perhaps actually provides a stimulation of the gonadotropic mechanism in the anterior lobe of the pituitary.

5) Advantages of the suggested method of treatment are: a) Only one injection is required, a fact which is of psychological importance to the patient. b) The anterior lobe of the pituitary is not inhibited by the small dose of estrogenic hormone administered (5 mg.). c) The intragluteal injections are well tolerated; secondary reactions, such as pain, have been observed in only a few cases.

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THE THIRTIETH ANNUAL MEETING OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

GENERAL INFORMATION

Headquarters: Red Lacquer Room of the Palmer House, Chicago, Illinois.

Registration: Everyone attending the meetings is requested to register. A fee of $1.00 will be charged non-members of the Association. Membership cards should be presented when registering.

The Scientific Sessions: The Scientific sessions will be held in the Red Lacquer Room of the Palmer House and programs will begin promptly on schedule. Papers presented at all meetings are planned for ten minutes and owing to the heavy schedule must be kept within this limit. Manuscripts of all papers should be submitted to the presiding officer or Secretary-Treasurer at the end of the presentation.

Annual Dinner: The Annual Dinner of the Association will be held on Friday evening, June 18th, at 7:30 o'clock in the Red Lacquer Room of the Palmer House, preceded by cocktails at 6:30 o'clock. Secure tickets at time of registration.

Council Meetings: There will be a meeting of the Council on Thursday afternoon, June 17th, at 2:00 o'clock, and a luncheon meeting on Friday June 18th.

Business Meeting: The Annual Business Meeting of the Association and Election of Officers will be held at 4:30 P.M., June 19th, in the Red Lacquer Room of the Palmer House.

Local Arrangements: Dr. Willard O. Thompson, 700 N. Michigan Ave., Chicago, Illinois, is in charge of the local arrangements for the meetings.

Secretary-Treasurer: Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma.

PROGRAM

FRIDAY, JUNE 18, 1948

8:30 a.m. Registration

I. 9:30 a.m. Red Lacquer Room

J. S. L. BROWNE, *presiding*

1. Pseudo-Glandular Disturbances.
   by Hugo R. Rony
2. Syndrome of Cyptorchidism, Heart Disease and Nevoid Dermatosis.
   by S. J. Glass
3. Constitutional Precocious Puberty Controlled by Androgen Therapy.
   by S. Charles Freed and Minnie Goldberg
4. A Study of the Biological Activity and the Magnitude of Endogenous Androgen Production in a Case of Andrenogenital Syndrome.
   by Anne C. Carter and Ephraim Shorr
5. Pseudohermaphrodism. Early and Late Recognition.
   by M. James Whitelaw
6. Clinical, Laboratory, Operative and Postmortem Observations in Infants and Children with Multiple Congenital Malformations (Turner's Syndrome, Ovarian Agenesis and Related Combinations).
   by Frank L. Plachte (introduced by Henry H. Turner)
7. A Syndrome Characterized by Hypercalcemia. Calcinosis, and Renal Insufficiency Following Prolonged Intake of Calcium and Alkali.
   by Charles H. Burnett, Robert R. Commons (by invitation), Fuller Albright and John E. Howard
8. Hypoparathyroidism, with Mental Troubles and Ectodermal Disorders.
   by Manuel Villaverde
9. Treatment of Far Advanced Inoperable Carcinoma of the Breast with Estrogens and Androgens.
   by Samuel G. Taylor, III, Danely Slaughter (by invitation) and Frederick W. Preston (by invitation)
10. Hormonal Factors Involved in the Regulation of Body Temperature During Menstrual Cycle and Pregnancy.
    by Charles L. Buxton and William B. Atkinson
11. The Effects of Certain Steroids—Intramuscular and Sublingual—On the Basal Body Temperature of the Adult Human Male.
    by Robert M. Perlman

II. 2:00 p.m. Red Lacquer Room

C. N. H. Long, *presiding*

12. A Simplified Hypophysectomized Rat Adrenal Ascorbic Acid Bioassay Method for Adrenocorticotrophin (A.C.T.H.); Specificity and Application to Preparative Problems.
    by Paul L. Munson, Alfred G. Barry, Jr. (by invitation), and F. C. Koch
13. Content of Adrenocorticotrophic Hormone (A.C.T.H.) in the Rat Pituitary Under Optimal and Stressful Environmental Conditions.
    by George Sayers, Marshal Merkin (by invitation) and J. N. Tortoreto (by invitation).
14. The Activation of the Adrenal Cortex by Insulin Hypoglycemia.
    by H. Gershberg (by invitation) and C. N. H. Long.
15. Influence of Adrenotrophic Hormone on Sodium Excretion in Hypophysectomized Rats.
    by Betty L. Rubin (by invitation) and Ralph I. Dorfman

16. Factors Influencing the Corticotrophin Production of the Anterior Pituitary.
    by Hans Selye
17. The Use of Andrenocorticotrophin as a Test of Adrenal Cortical Reserve.
    by George W. Thorn, Peter H. Forsham (by invitation), Lillian Recant (by invitation) and A. Gorman Hills (by invitation)
18. Observations on the Pituitary-Adrenal Response Following Epinephrine Infusion in Man.
    by Lillian Recant (by invitation), Peter H. Forsham (by invitation) and George W. Thorn
19. Fate and Metabolic Action of Intravenously Administered Adrenocorticotrophic Hormone (A.C.T.H.).
    by Thomas W. Burns (by invitation), George Sayers, Frank H. Tyler (by invitation), B. V. Jager (by invitation), T. B. Schwartz (by invitation), Emil L. Smith (by invitation) and L. T. Samuels
20. Metabolic Changes Following the Administration of Pituitary Adrenocorticotrophic Hormone (A.C.T.H.) to Normal Humans.
    by H. T. McAlpine (by invitation), E. H. Venning, L. Johnson (by invitation), V. Schenker (by invitation), M. M. Hoffman and J. S. L. Browne
21. The Effect of Adrenocorticotrophin on Antibody Levels in Normal Human Subjects.
    by P. H. Herbert and J. A. de Bries (introduced by J. S. L. Browne)
22. A Comparison of the Effect on Bone Formation of the Hyperadrenocorticism of Cushing's Syndrome with that Induced by Adrenocorticotrophic Hormone (A.C.T.H.).
    by Frederic C. Bartter (by invitation), Anne P. Forbes and Fuller Albright
23. Adrenal Cortical Unresponsiveness in Patients with Gastric Cancer.
    by Edward C. Reifenstein, Jr., N. F. Young (by invitation), Aurelia Potor (by invitation), Benedict Duffy (by invitation) and F. Homburger (by invitation)
24. The Excretion of Adrenal Metabolites in Human Urine.
    by Konrad Dobriner, Seymour Lieberman (by invitation) and C. P. Rhoads (by invitation)

III. Annual Dinner, Friday, June 18.

7:30 P.M.—Red Lacquer Room, Palmer House

Presentation of E. R. Squibb and Sons Award for 1948
Presentation of Ciba Award for 1948
Presentation of Ayerst, McKenna and Harrison Fellowship for 1948.
by Warren O. Nelson, Chairman of the Committee on Awards 1947–48
President's Address: C. N. H. Long, Yale University

SATURDAY, JUNE 19, 1948

IV. 9:00 a.m. Red Lacquer Room

R. G. Hoskins, *presiding*

25. Preparation of Crystalline Growth Hormone.

by Jacob B. Fishman (by invitation), Alfred E. Wilhelmi (by invitation) and Jane A. Russell

26. The Influence of Purified Growth Hormone on Fasting Metabolism.
by Clara M. Szego and Abraham White

27. Unpredictable Effects of Growth Hormone Preparations on Nitrogen Storage.
by Paul Bartlett (by invitation) and Oliver H. Gaebler

28. Studies in Growth. I. The Effects of Androgen in Gigantism and Acromegaly.
by Laurence W. Kinsell, George D. Michaels (by invitation), Choh Hao Li (by invitation) and William E. Larsen (by invitation)

29. The Effect of Iodine Injections on Energy Metabolism and Plasma Protein-Bound Iodine of Rats.
by S. B. Barker and H. J. Lipner (by invitation)

30. The Effect of Pituitary and Non-Pituitary Gland Factors on the Formation of Intracellular Colloid Droplets in the Thyroid Gland in Vivo and in Vitro.
by Samuel Dvoskin

31. Inactivation of the Exophthalmic, Thyrotropic and Ketogenic Principles of Anterior Pituitary Extract by Iodination.
by William McK. Jefferies

32. Newer Methods of Antagonizing Hyperthyroidism.
by Robert H. Williams, Rene F. Tagnon (by invitation), Herbert Jaffe, (by invitation), Beverly T. Towery (by invitation) and Walter F. Rogers (by invitation)

33. The Use of Radioactive Iodine (I 131) in the Study of Normal and Disordered Thyroid Function in Man.
by Sidney C. Werner and Edith Quimby (by invitation)

34. The Effect of Thyroid Stimulating Hormone on the Function of Human Normal and Malignant Thyroid Tissue.
by J. B. Trunnell (by invitation), R. W. Rawson, L. D. Marinelli (by invitation) and Ruth Hill (by invitation)

35. The Relation Between Infant Birthweight and Subsequent Development of Maternal Diabetes Mellitus.
by Joseph P. Kriss and Palmer H. Futcher (introduced by Cyril M. MacBryde)

V. 2:00 p.m. Red Lacquer Room

A. T. Kenyon, *presiding*

36. Absorption and Excretion of Chorionic Gonadotrophin When Administered Intramuscularly to Women.
by J. T. Bradbury and Willis E. Brown

37. The Renal Clearance of Chorionic Gonadotrophic Hormone in Pregnancy and in Neoplasm of the Testis.
by C. F. Gastineau (by invitation), A. Albert and L. M. Randall (by invitation)

38. The Metabolic Response to Chorionic Gonadotrophin in Young Men.
by Kathryn Knowlton (by invitation) and Allan T. Kenyon

39. Blood Gonadotrophin Studies During Pregnancy in Relation to the Fetal Sex.
by H. E. Nieburgs and Robert B. Greenblatt

40. On the Principal Estrogenic Constituents of the Urine of the Stallion.
by Louis Levin

41. Mechanism of Inactivation of α-Estradiol by Rat Liver in Vitro.
by R. H. deMeio (by invitation), A. E. Rakoff, A. Cantarow and K. E. Paschkis

42. Cozymase in the Hepatic Inactivation of α-Estradiol.
by Richard L. Coppedge (by invitation), Albert Segaloff, Herbert Sarett (by invitation) and Aaron Altshul (by invitation)

43. Interference with Estrogen-Induced Growth in the Female Genital Tract by Folic Acid.
by Roy Hertz

44. The Relation of Folic Acid to the Action of Estrogens.
by Irene T. Kline (by invitation) and Ralph I. Dorfman

45. Fluorescent Phenomena of the Vulva Associated with Sex Hormone Metabolism.
by M. Sydney Margolese

46. Testicular Deficiency: A Clinical and Pathological Study.
by R. Palmer Howard, Ronald C. Sniffen (by invitation) and Fred A. Simmons

47. A Comparison of the Effect of Various Androgens on the Temporal Muscle and Organs of the Castrated Male Guinea Pig.
by Charles D. Kochakian and Jane Harrison Humm (by invitation)

VI. Annual Business Meeting

5:00 P.M. Red Lacquer Room

Papers to be Read by Title

48. The Use of Whole Adrenal Cortical Extract in Experimental Infections.
by Erwin P. Vollmer, James D. Gillmore (by invitation), Leo Cravitz (by invitation) and J. E. Samsell (by invitation).

49. The Work Performance of Adrenalectomized Rats Given Continuous Intravenous Infusions of Glucose.
by Dwight J. Ingle and James E. Nezamis (by invitation)

50. Sublingual Administration of Desoxycorticosterone Acetate in the Treament of Addison's Disease.
by Evelyn Anderson, Lawrence W. Kinsell, Troy C. Daniels (by invitation) and Edward Henderson

51. Excretion of Adrenal Metabolites Following the Administration of Adrenocorticotrophic Hormone to Normal Human Subjects.
by Eleanor H. Venning, V. E. Kazmin (by invitation), Miriam Ripstein (by invitation), H. T. McAlpine (by invitation) and M. M. Hoffman

52. The Effect of 11-Dehydrocorticosterone on Fecal Fat Excretion.
by Grace E. Bergner (by invitation), Roger A. Lewis (by invitation), Frances W. Stout (by invitation), George W. Thorn and Kendall Emerson, Jr.

53. An Estimation of the Quantity of 11-17-Oxysteroid Excretion by the Human Adrenal Stimulated by ACTH.
by A. Gorman Hills (by invitation) and George W. Thorn

54. Isolation of Urinary Steroids from a Patient with Apparent Adrenal Involvement.
by A. M. Miller (by invitation) and Ralph I. Dorfman

55. The Effect of Adrenalectomy and Desoxycorticosterone Acetate Administration upon the ECG Response of the Rat to Cardiac Glycosides.
by Herbert S. Kupperman, Joseph G. Benton (by invitation) and Arthur C. DeGraff (by invitation)

56. Activation of the Adrenal Cortex in Human Subjects Following Electroconvulsive Therapy (E.C.T.) and Psychomotor Stress.
by R. A. Cleghorn and A. J. Goodman (by invitation), B. F. Graham, M. H. Jones and N. K. Rublee

57. Effect of Adrenal Cortical Compounds on Electrolyte Metabolism of a Patient with Addison's Disease During High Sodium Chloride Intake.
by Aurelia Potor (by invitation), Nelson F. Young (by invitation), F. Homburger (by invitation) and Edward C. Reifenstein, Jr.

58. Nitrogensparing (Protein-Anabolic) Action of Thyroid Hormone.
by J. Rupp (by invitation) and K. E. Paschkis

59. Thiouracil Effect on Plasma and Liver Protein Concentrations.
by James H. Leathem

60. Radioiodine Uptake by the Thyroid as an Aid in Differential Diagnosis.
by S. M. Seidlin, E. Oshry (by invitation), I. Rossman (by invitation) and L. Leiter (by invitation)

61. Thyroid Uptake of Radioactive Iodine in the Normal and Hypometabolic Human.
by Martin Perlmutter (by invitation) and Peter H. Forsham (by invitation)

62. Cellular Involution in the Thyroid.
by Nathan B. Friedman

63. Methyl Thiouracil in the Treatment of Thyrotoxicosis.
by Grosvenor W. Bissell, John M. Benny (by invitation), Victor Totah (by invitation) and Florence Gilbert (by invitation)

64. Modification of the Estrual Cycle of the Ewe by the Use of Progesterone; the Effect Upon Subsequent Ovulation Rate and Fertility of Ova.
by R. H. Dutt (by invitation) and L. E. Casida

65. Effects of Various Estrogenic Preparations on the Vaginal Mucosa.
by Mildred Vogel (by invitation), Thomas H. McGavack and Joseph Mellow (by invitation)

66. The Use of the Vaginal Smear in the Assay of Estrogens Given Orally or Intramuscularly.
by Willis E. Brown and J. T. Bradbury

67. The Similarity of Estrogenic Effect in Premenstrual Tension, Menstrual Anomalies, Chronic Cystic Mastitis and Cancer of the Breast.
by Joseph H. Morton
68. Hyperestrogenism Treated with Lactogenic Hormone (Prolactin).
by Manuel Villaverde
69. The Factor of Rhythm in Experimental Menstruation.
by Doris H. Phelps
70. Hormonal Pellets in the Management of the Menopausal Syndrome.
by Robert B. Greenblatt and Roland R. Suran (by invitation)
71. The Effect of Hypophysectomy on the Ovulability of the Ovarian Follicle of the Domestic Hen.
by Irving Rothchild and R. M. Fraps
72. Prognostic Value of Pregnanediol Excretion in Threatened Abortion with Special Reference to the Effects of Diethylstilbestrol.
by A. R. Abarbanel
73. Further Studies on the Endometrial Cups of the Pregnant Mare.
by H. H. Cole and G. H. Hart
74. Inactivation of Posterior Pituitary Antidiuretic Hormone of the Liver.
by W. J. Eversole, J. H. Birnie (by invitation) and Robert Gaunt
75. The Estimation of Dehydroisoandrosterone and Related Compounds in Human Urine by a Modification of the Pettenkoffer Reaction.
by Richard L. Landau and Kathleen Lugibihl (by invitation)
76. Clinical Evaluation for 17-Ketosteroids by the Rapid Method.
by T. H. McGavack, S. Kenigsberg, A. M. Shearman and K. J. Drekter
77. The Application of Paper Partition Chromatography to Ketosteroids.
by Robert B. Burton (by invitation), Alejandro Zaffaroni (by invitation) and E. Henry Keutmann
78. A Rapid Modification of the Zimmermann Test for Ketosteroids.
by Sidney Pearson and Sylvester Giaccone (by invitation)
79. A Fluorometric Method for the Determination of Estrone and Estradiol in Human Urines.
by Joseph W. Jailer
80. A Clinical Bio-Assay for Chorionic Gonadotrophin.
by A. Albert
81. Specificity of a Colorimetric Method for Dehydroisoandrosterone in Urine Extracts.
by Paul L. Munson, Mary Ellen Jones (by invitation), Philip J. McCall (by invitation) and T. F. Gallagher (by invitation)
82. The Colorimetric Determination of Sodium and Its Application in the Study of Sodium and Chloride Balance.
by Joseph W. Goldzieher and Gilbert Stone (by invitation)
83. Depression of Lymphocyte Count After Orally Administered Glucose.
by Paul A. Marks (by invitation), Dorothy T. Marks (by invitation) and Joseph W. Jailer
84. Pitfalls in the Diagnosis of Diabetes.
by Bernard A. Watson
85. Electrolyte Balance Studies in the Uncontrolled and Controlled Diabetic State.

by Jonas Weissberg (by invitation), Thomas H. McGavack, A. M. Shearman (by invitation) and I. J. Drekter

86. The Role of the Endocrine Glands in Body Temperature Regulation.
by H. E. Nieburgs and Robert B. Greenblatt

87. The Lipogenic Activity of Propylthiouracil, Triphenylchloroethylene and Hexestrol in Chickens.
by R. George Jaap

88. The Influence of the Pituitary Gland on Blood Vessel Development. The Effect of Concentrated Pituitary Extract on the Isolated Kidney.
by Robert C. Moehlig and Louis Jaffe (by invitation)

89. Results of Prolonged Medical Treatment of Obesity with Diet Alone, Diet and Thyroid Preparations, and Diet and Amphetamine.
by David Adlersberg and Martin E. Mayer (by invitation)

90. The Urethral Smear in the Normal Human Male.
by Mildred T. Vogel (by invitation), Thomas H. McGavack and Henry Kammandel (by invitation)

91. The Specific Ovarian Hyperemic Inducing Effect of Luteinizing and Luteotrophic Hormones.
by Herbert S. Kupperman, W. H. McShan and Roland K. Meyer

PROGRAM OF THE 1948 LAURENTIAN HORMONE CONFERENCE

Forest Hills Hotel, Franconia, New Hampshire

Because of limited accommodations, attendance is by invitation, but the Committee on Arrangements will receive applications for membership until June 15, 1948. Applications should be addressed to: Dr. Gregory Pincus, Chairman, Committee on Arrangements, 222 Maple Avenue, Shrewsbury, Massachusetts.

I. Steroid Hormone Metabolism "in vivo" and "in vitro"

Some aspects of Progesterone Metabolism
Dr. G. F. Marrian, *University of Edinburgh*
Monday, Evening, September 13

Recent Developments in Our Knowledge of Estrogen Metabolism
Dr. R. D. H. Heard and Mrs. J. C. Saffran, *McGill University*
Tuesday Morning, September 14

The Metabolism of Androgens by Tissues
Dr. Leo T. Samuels, *University of Utah*
Tuesday Morning, September 14

The Metabolism of Estrogens with Particular Emphasis on Clinical Aspects of Physiology and Function of Ovarian Hormones
Dr. Albert Segaloff, *Alton Ochsner Medical Foundation*
Tuesday Evening, September 14

II. The Role of Hormones in Tissue and Body Metabolism

The Antihormone Problem in Endocrine Therapy
Dr. James H. Leathem, *Rutgers University*
Wednesday Morning, September 15

Integration of the Metabolic Effects of Adrenal Cortical, Thyroid and Growth Hormones
Dr. Abraham White, *University of California at Los Angeles*
Wednesday Morning, September 15

The Alterations in Metabolism Incident to Administration of Insulin, Adrenalin and Thyroid Substances, Studied with the Aid of Isotopes

DR. DEWITT STETTEN, JR., *Harvard University Medical School*

Wednesday Evening, September 15

The Pancreas as the Guardian of the Liver

DR. CHARLES H. BEST, *University of Toronto*

Thursday Morning September 16

Metabolic Changes in Man Following Adrenal and Pituitary Hormone Therapy

DR. GEORGE W. THORN, *Harvard University Medical School*

Thursday Morning, September 16

III. NEUROHUMORAL-HYPOTHALAMIC RELATIONSHIPS

Adrenal Function in Mental Disease

DR. GREGORY PINCUS, Dr. HUDSON HOAGLAND, DR. HARRY FREEMAN and MR. FRED ELMADJIAN, *Worcester Foundation for Experimental Biology*

Thursday Evening, September 16

Manifestations of Altered Autonomic and Humoral Functions in Psychoneuroses

DR. ROBERT A. CLEGHORN, and DR. B. F. GRAHAM, *McGill University*

Friday Morning, September 17

Effects of Hypothalamic Lesions on Water and Energy Metabolism in the Rat

DR. JAMES A. F. STEVENSON, *Yale University*

Friday Morning, September 17

IV. THYROID PHYSIOLOGY AND FUNCTION

Physiologic Reactions of the Thyroid Stimulating Hormone

DR. RULON W. RAWSON and DR. WILLIAM L. MONEY, *Massachusetts General Hospital*

Friday Evening, September 17

The Metabolism of Iodine as Disclosed by the Use of Radioiodine (I131)

DR. F. R. KEATING, JR., and DR. ALEXANDER ALBERT, *The Mayo Clinic*

Saturday Morning, September 18

Radioiodine as a Diagnostic and Therapeutic Tool in Clinical Medicine

DR. S. M. SEIDLIN, *The Montefiore Hospital*

Saturday Morning, September 18